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13th Annual Report

National Institutes of Health Program in Biomedical and Behavioral Nutrition Research and Training

Fiscal Year 1989



U.S. Department of Health and Human Services
Public Health Service
National Institutes of Health

13th Annual Report

National Institutes of Health Program in Biomedical and Behavioral Nutrition Research and Training

Fiscal Year 1989



NIH Nutrition Coordinating Committee
Division of Nutrition Research Coordination

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EXECUTIVE SUMMARY

Nutrition research represents a cross-cutting scientific endeavor that seeks to assess the consequences of food or nutrient intake in the intact organism and the metabolic and behavioral mechanisms involved. As such, it encompasses studies at the cellular and subcellular levels; elucidation of the metabolic function of nutrients in both animals and humans; examination of genetic-nutrient-environmental interactions; and studies of the role of diet in the maintenance of health and the prevention of disease in humans, including clinical trials, epidemiological studies, metabolic studies, surveillance, and nutritional status monitoring studies. All of these are activities of the NIH Program in Biomedical and Behavioral Nutrition Research and Training.

Over the past 13 years, this report, published annually since 1977, has emphasized the coordination of nutrition research at NIH, the activities of the Nutrition Coordinating Committee (NCC), the highlights of the nutrition research program and associated program development, and the fiscal year obligations in nutrition research and training. These topics also are featured in this year's report detailing highlights of nutrition research at NIH and the activities of the NCC.

The NCC was established in 1975 in the NIH Office of the Director, in recognition of the importance of nutrition as a cross-cutting issue at NIH. In FY 1989, the NCC consisted of representatives from 13 NIH institutes, 2 centers, and 2 divisions, with liaison representatives from other NIH offices, as well as from other Federal agencies. Since 1988, the NCC has been part of the Division of Nutrition Research Coordination (DNRC) in the Office of the Director. The DNRC was created to firmly establish the trans-NIH coordination of nutrition research and training as a permanent and identifiable position within the NIH and to recognize the additional responsibilities acquired over time by the NCC office. The NIH nutrition program continues to be coordinated through the NCC, which operates as an NIH-wide forum and locus for the

coordination of research efforts, helping the NIH to avoid duplication of effort, and to speak with one voice in nutrition matters. The NIH collaborates with other U.S. government organizations, both within and outside the Department of Health and Human Services (DHHS); with academic institutions; with private sector firms; and with investigators in other countries who are developing and implementing research programs of mutual interest. Fostering cooperation and collaboration in nutrition research and training within the NIH is a major function of the DNRC and its NCC. The coordinated trans-NIH activities, as well as the collaborative interagency activities at the DHHS and Federal levels, of the NCC and DNRC are detailed in section 1 and the appendices of this report.

Each institute, center, and division (ICD) of the NIH plays a unique role in support of nutrition research, as each funds those areas of nutrition science related to its own particular research mission. The combination of the research areas thus represented encompasses the entire spectrum of modern biomedical nutrition research, from basic to applied, providing a diversity which is one of the NIH's greatest assets. Highlights of the individual ICD nutrition research programs are presented in section 2.

This report is not designed to give a comprehensive description of each of the more than 2,400 nutrition research and training projects supported by the NIH during FY 1989. However, we have tried to convey the range and diversity of these projects by presenting selected research highlights which involved peer-reviewed studies funded by many different institutes in section 3 of this report. Research on the prevention in minority groups of some of the most common nutrition-related disorders affecting our population—obesity, cardiovascular disease, diabetes, and osteoporosis—is highlighted, as is nutrition in rare diseases and conditions. The interdisciplinary and collaborative nature of nutrition research is emphasized in reports on

research conducted within the Clinical Nutrition Research Units, the General Clinical Research Centers Program, other centers, and the Animal Resources Program. International collaborations and research on national nutrition monitoring also are highlighted.

Finally, information on the fiscal year obligations in nutrition research and training is provided in section 4. In FY 1989, as in previous years, the NIH led all Federal agencies in financial support of biomedical nutrition research and training, for a total of \$287 million. The NIH expenditures have consistently represented between 70 and 73 percent of all Federal expenditures and between 92 and 95 percent of all DHHS expenditures in biomedical nutrition research and training. The NIH expenditures for nutrition research and training have increased steadily during the past decade, growing from \$134 million in FY 1979 to \$287 million in FY 1989. This represents an increase of 114 percent (or 12 percent if dollars are adjusted for inflation). The NIH nutrition research and training dollars have consistently represented approximately 4 percent of total NIH obligations since 1977.

Important discoveries over the last decade in molecular biology, genetics, and immunology have provided new opportunities for advances in the biomedical sciences. The techniques for addressing the fundamental questions about the nature of living organisms that have evolved from these discoveries are now beginning to be applied to nutritional studies. Their further application should advance biomedical nutrition research at an unprecedented pace and have a major impact on health.

ACKNOWLEDGMENTS

The activities of the NIH Nutrition Coordinating Committee (NCC) would not be possible without the support and commitment to nutrition research of the institute, center, and division (ICD) members and alternates to the committee. Each year, the representatives to the NCC devote personal time and effort over and above their full-time ICD responsibilities to make this annual report possible. The following individuals deserve special acknowledgment for their contributions this year: Dr. Peter Greenwald, Dr. Ritva Butrum, and Dr. Mark Messina, NCI; Nancy Ernst and Karen Donato, NHLBI; Dr. Joseph Ciardi and Joan Wilentz, NIDR; Dr. Van Hubbard and Dr. Donald Murphy, NIDDK; Patricia Turner and Mary Miers, NINDS; Dr. Eugene Zimmerman and Dr. Daniel Mullally, NIAID; Dr. Yvonne Maddox, NIGMS; Dr. Ephraim Levin, NICHD; Dr. Barbara Underwood, NEI; Dr. Thorsten Fjellstedt and Dr. Michael Galvin, NIEHS; Dr. Ann Sorenson and Dr. Judith Hallfrisch, NIA; Dr. Stephen Heyse and Dr. Joan McGowan, NIAMS; Dr. Jack Pearl, Dr. Marin Allen, and Helen Simon, NIDCD; Dr. Moira Shannon and Dr. John Chah, NCNR; Dr. Kenneth Bridbord and Dr. Ferdinand Hui, FIC; Dr. Harriet Gordon, NCRR; Gloria Stables, CC; Judy Mahaffey, DCRT; Betsy Duane, DLA; and Dr. Ai Lien Wu and Sue Meadows, DRG.

The timely publication of this report would not have been possible without the extraordinary cooperation and assistance of the many individuals from Editorial Operations Branch; Printing and Reproduction Branch, DTS, ORS; Administrative Office staff, OD; and many other individuals at the NIH who made special efforts for this report.

On behalf of the NCC members I wish to thank the staff of the Division of Nutrition Research Coordination (DNRC) for their contributions in the preparation of this report. A special acknowledgment is due to Patricia Blessing, nutrition science writer, and Dr. Susan Pilch, deputy director, who accomplished the task of coordinating, writing, and overseeing production of this annual report despite impossible deadlines. Thanks also are due to Melissa Workman for data retrieval and analysis, to Ellen Mirin for editorial assistance, and to Lucille Wilfand and Margaret Murphy for their excellent secretarial support.

Darla E. Danford, M.P.H., D.Sc.
Chairperson
Nutrition Coordinating Committee
Director
Division of Nutrition Research Coordination

Section 1. Coordination of Nutrition Research and Training



COORDINATION OF NUTRITION RESEARCH AND TRAINING

NIH'S INVESTMENT IN NUTRITION RESEARCH

The mission of the NIH is to improve the health of the nation by increasing the understanding of processes underlying human health, disability, and disease; advancing knowledge concerning the health effects of interactions between man and the environment; and developing and improving methods of preventing, detecting, diagnosing, and treating disease. To carry out its mission and legislative mandates, the NIH currently is organized into an Office of the Director, 13 research institutes, 2 service divisions (Division of Research Grants and Division of Computer Research and Technology), 5 centers (the Clinical Center, the Fogarty International Center, the National Center for Nursing Research, the National Center for Human Genome Research, and the National Center for Research Resources), and the National Library of Medicine. Figure 1 shows the components of the NIH.

The NIH's commitment to the field of biomedical nutrition research is reflected by the unique contribution each institute, center, and division (ICD) makes in support of nutrition research related to its own particular mission. As a whole, these research efforts encompass the entire spectrum of nutrition research, ranging from determining individual nutrient requirements of the cell to identifying diet and risk factors for diseases. NIH's primary nutrition mission lies in biomedical and behavioral research and training, but also supports nutrition education as an integral part of many research programs.

Through these components, the NIH is the major agency within the Federal government that supports research and training in nutrition as it relates to health maintenance, disease treatment and prevention, and human development throughout the life cycle. In FY 1989, the NIH led all Federal agencies in financial support of nutrition research and training for a total of \$287 million. The legislative authority for nutrition at the NIH is presented in appendix A.

DIVISION OF NUTRITION RESEARCH COORDINATION

An important addition to the NIH organization in 1988 was the establishment of the Division of Nutrition Research Coordination (DNRC) within the Office of Disease Prevention (ODP), Office of the Director (OD), as shown in figure 2. The new division enhanced and expanded NIH's goals to coordinate nutrition research programs and training, avoid duplication of research efforts among ICDs, and present nutrition information uniformly. The DNRC advises the Director of the NIH and the Associate Director for Disease Prevention on nutrition research. The DNRC represents the NIH at the department and interagency level on committees addressing nutrition research and nutrition policy issues.

The coordination activities by the DNRC involve three major categories: coordinated trans-NIH activities; collaborative inter-agency activities at the DHHS level; and collaborative interagency activities at the Federal level. At the NIH level, the DNRC coordinates nutrition activities through the Nutrition Coordinating Committee (NCC) and its Nutrition Education Subcommittee (NES). The DNRC also relies extensively on the expertise of these two committees in its collaborative nutrition activities at the DHHS and Federal level.

Coordination of Trans-NIH Activities

NIH Nutrition Coordinating Committee - NCC

The NCC, established in 1975, operates as an NIH-wide forum and locus to review, stimulate, and encourage the support of nutrition research and training in order to better define the role of nutrition in the promotion and maintenance of health and in the prevention and treatment of disease. The functions and responsibilities of the NCC now are encompassed within the framework of the DNRC.

Currently, the NCC consists of representatives from 13 institutes and 4 centers at the NIH;

Figure 1. Components of the National Institutes of Health

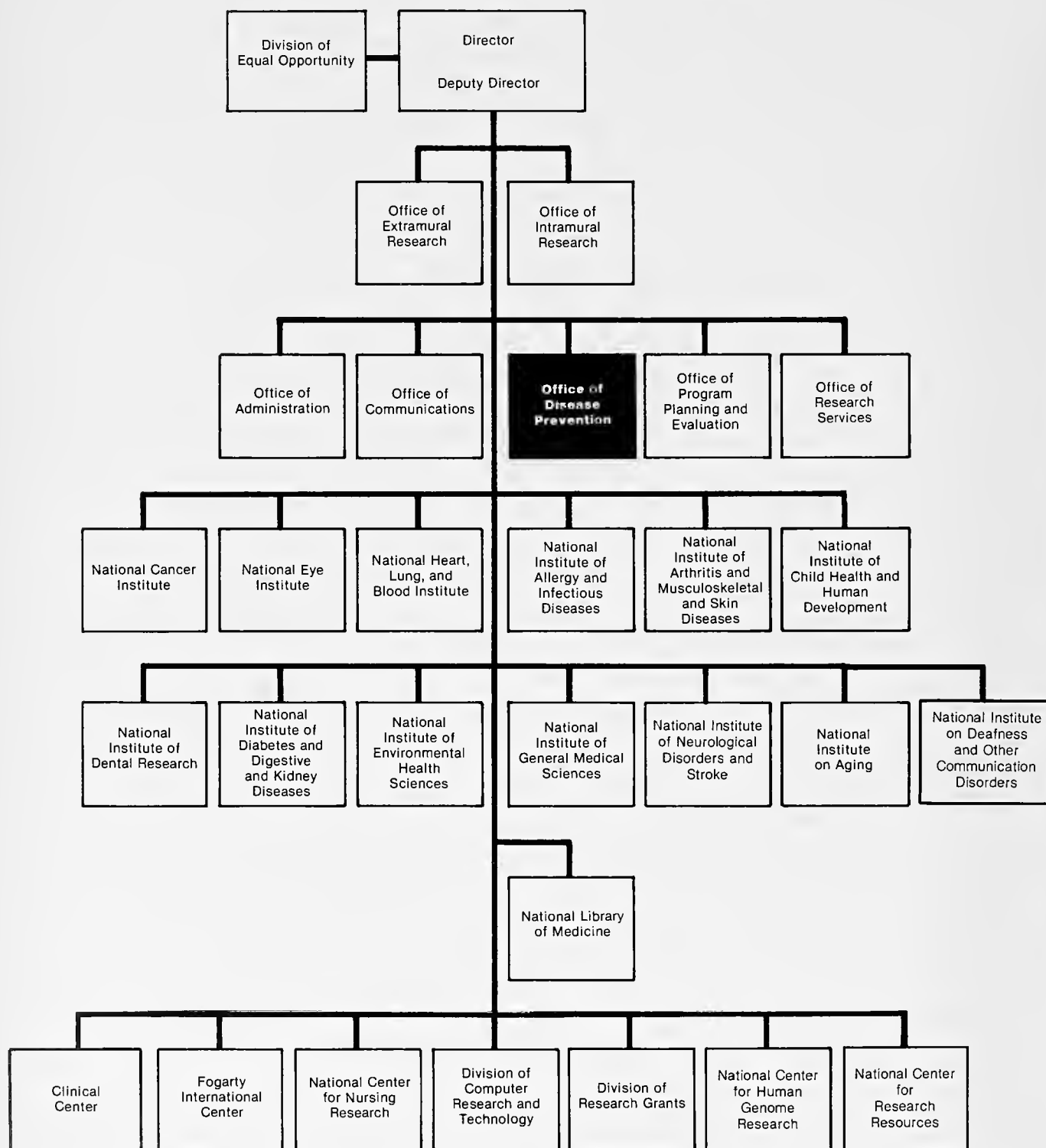
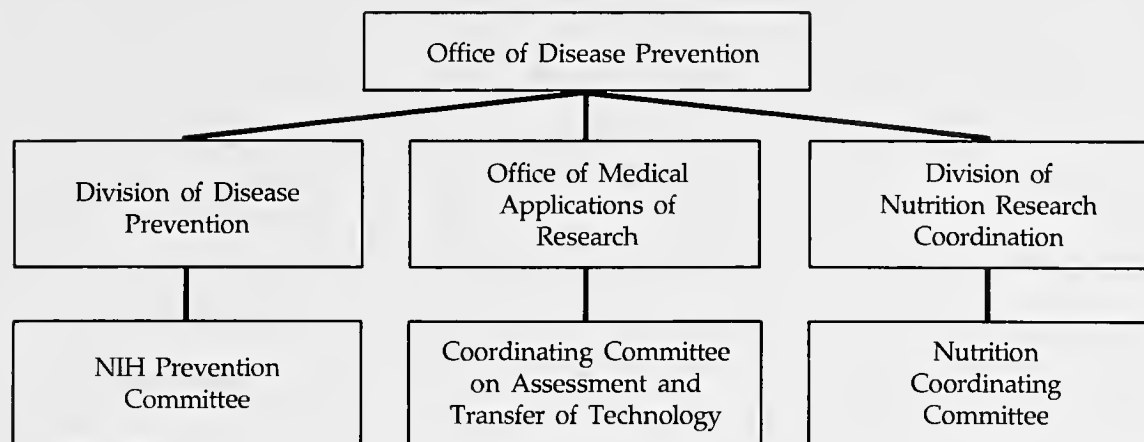


Figure 2. Components of the Office of Disease Prevention



during FY 1989, it consisted of representatives from 13 institutes, 2 centers, and 2 divisions. Additional NIH offices and other agencies of the Department of Health and Human Services (DHHS) and U.S. Department of Agriculture (USDA) have liaison representatives to the committee. A list of NCC members, alternates, and liaison representatives and of the NCC's Nutrition Education Subcommittee members as of September 1, 1989, can be found in appendix B.

The NCC provides a locus for the review and coordination of research and training efforts related to nutrition and for the development of the NIH Program in Biomedical and Behavioral Nutrition Research and Training. The NCC has published an annual report of this program since 1977. The description of NIH-wide activities contained herein constitutes the *13th Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training, FY 1989* (NIH Publication No. 90-2092, 1990). The NCC forum minimizes the duplication of effort among the institutes and identifies areas where research training and development can be enhanced. This is accomplished through several different

approaches, such as developing program announcements (PAs), requests for applications (RFAs), and requests for proposals (RFPs); appendix C lists PAs, RFAs, and RFPs in nutrition published in FY 1989.

The NCC plays a key role in the development of nutrition research policy at the NIH. Currently, NIH's nutrition research policy consists of eight areas. Research is emphasized in four of these areas: clinical nutrition throughout the life cycle, and nutritional factors in the development of disease, prevention of disease, and treatment of disease. The other four areas are related to education and technology transfer: the transfer of modern nutrition technology, nutrition education for professionals and the public, nutrition research training and research manpower development in nutrition, and trans-NIH and interagency coordination.

The DNRC and its NCC prepare and review many trans-NIH and interagency nutrition-related documents. In FY 1989, the DNRC and its NCC prepared and reviewed the updated brochure *Nutrition Research at the NIH* (NIH Publication No. 90-2611, 1990) that provides

descriptions of nutrition-related biomedical research programs of the institutes and centers to inform extramural investigators and potential grantees about nutrition research opportunities. The NCC's activities in reviewing interagency publications and documents can be found in the two sections that follow on collaborative interagency activities.

Definition of Nutrition Research at the NIH

The term *nutrition research* includes studies designed to assess the consequences of food or nutrient intake and utilization in the intact organism, including humans, and the metabolic and behavioral mechanisms involved. These studies encompass investigation of nutrient variables at the cellular or subcellular level. This definition also includes:

- Research designed to elucidate the metabolic role or function of nutrients in both animal models and humans.
- All studies concerned with genetic-nutrient-environmental interactions where a nutrient is a variable.
- Dietary studies expected to produce significant changes in health status, including the maintenance of health and the treatment of disease in humans. Such studies might include clinical trials, epidemiological studies, metabolic studies, surveillance, and nutritional status monitoring studies.

The NCC also sponsors conferences and workshops in nutrition; in FY 1989, the committee sponsored 17 conferences, which are shown in appendix D. In addition, the NCC sponsors scientific seminars to coincide with its regular meetings. These special presentations on topics of current interest to NCC members are made by a variety of researchers and representatives of professional groups such as NIH grantees from the academic community, NIH investigators, and scientists from other

Federal agencies. In FY 1989, the NCC sponsored six seminars; the abstracts are listed in appendix E.

The NCC liaison representatives offer a variety of assistance to the committee. The representative from the Warren Grant Magnuson Clinical Center provides information on research conducted in clinical nutrition and food service management. The liaison representative from the Division of Computer Research and Technology designed and implemented the Human Nutrition Research and Information Management (HNRIM) System, which is operated by the DNRC. The Division of Legislative Analysis staff member tracks information on proposed legislation affecting biomedical nutrition research and training. The representative from the Division of Research Grants provides information on the number and types of nutrition-related applications submitted to the NIH and reviews new mechanisms and policies. From the National Library of Medicine, the staff member provides information on accessing scientific literature related to nutrition and other biomedical sciences. The representative from the Office of Communications assists the NCC by referring inquiries on nutrition-related topics from the media and public to appropriate NIH offices. The NCC also is assisted by its interagency liaison representatives from ADAMHA, CDC, FDA, HRSA, NCHS, ODPHP, and USDA.

Nutrition Education Subcommittee - NES

The major responsibility of the NES is to review nutrition education publications written for the public to assure institute-wide scientific accuracy and consistency in providing dietary guidance information (see appendix F for NES review procedures). The mandate of the NES also includes the following activities: identify mechanisms to improve nutrition education activities for professionals and the public; initiate, develop, or review nutrition activities or programs directed to NIH employees such as activities to commemorate National Nutrition Month; and serve as advisors on nutrition issues,

programs, or publications of other Government agencies when pertinent to the interests of the NIH and requested by the NCC, the director, or both.

The NES and the NCC were extensively involved in reviewing *The Surgeon General's Report on Nutrition and Health*, which was published in July 1988 (DHHS [PHS] Publication No. 88-50210). In FY 1989, the NES reviewed a number of NIH nutrition education materials, including the NCI publication *Helping Your Child Eat Well During Cancer Treatment: A Parent's Guide*; nutrition information in NHLBI's *Kit '90: The Right Moves*; the NICHD publication *Understanding Gestational Diabetes—A Practical Guide to a Healthy Pregnancy*; and articles by the NIA on "Fiber and Heart Disease" and "The Fallacies of Food Fads for Older People." NIH nutrition publications for the public reviewed by the NES are listed in appendix G.

Collaborative Interagency Activities at the DHHS Level

Nutrition Policy Board - NPB

Chair:	Deputy Assistant Secretary for Health, ODPHP
Members:	NIH (DNRC), OHDS, CDC, HRSA, FDA, FSA, ADAMHA, IHS, AOA

NPB Subcommittee on Dietary Guidance

Chair:	Deputy Assistant Secretary for Health, ODPHP
Members:	NIH (DNRC), FDA, OHDS, AOA, HRSA, CDC, IHS
Liaison Members:	NIH (NCI, NHLBI), USDA (HNIS)

The NPB provides a forum to coordinate nutrition policy development and implement programs within the DHHS. The NPB facilitates the exchange of information on

DHHS nutrition activities, provides advice and counsel to the Secretary of the DHHS on major nutrition policy issues, and serves as the focal point for nutrition policy matters with other Federal agencies as well as non-Federal agencies and organizations. The DNRC represents the NIH on the NPB; NIH liaison members of the NPB's Subcommittee on Dietary Guidance include the NCI and NHLBI.

The NPB's Subcommittee on Dietary Guidance coordinates DHHS activities that offer dietary guidance information for healthy American populations. The subcommittee ensures departmental consistency with the principles established in the *Dietary Guidelines for Americans*; coordinates DHHS portions on dietary guidance; facilitates consistency of dietary guidance information from all Federal sources; and exchanges information on ways to improve the effectiveness of dietary guidance publications.

In FY 1989, members of the NPB reviewed the second report on *Nutrition Monitoring in the United States: An Update Report on Nutrition Monitoring* (DHHS Publication No. [PHS] 89-1255) prepared by the Life Sciences Research Office, FASEB. Committee members reviewed the report for adherence to the scope of work and for technical accuracy. Another major activity of the NPB and its subcommittee in FY 1989 was updating the third edition of the *DHHS/USDA Dietary Guidelines for Americans*. The DNRC, NIH members of the NCC, the NES, and other NIH staff participated in reviewing this publication for the NIH. The new Guidelines are expected to be published in 1990.

DHHS Task Force on the Nutrition Objectives for the Nation

Lead Agencies:	NIH (DNRC), FDA
Members:	CDC, HRSA, IHS, NCHS, ODPHP
Liaison Members:	APHA, ASTPHNPD, DOD, USDA

A decade ago, the Surgeon General published a broad list of health objectives that were to be achieved by 1990 for improved health status in priority areas related to health promotion and disease prevention. These objectives have been used as a basis for developing a new set of health objectives for the next decade. Nutrition continues to be a separate priority area of these objectives, reflecting the growing consensus about the important role nutrition plays in health promotion and disease prevention.

The preparation of the Year 2000 objectives is well under way, and the objectives are expected to be released in the fall 1990 in the publication *Healthy People 2000: National Health Promotion and Disease Prevention Objectives*. The Year 2000 objectives expand and revise priority areas of the 1990 objectives, with additional focus on topics such as acquired immunodeficiency syndrome (AIDS), and increased attention to improvements in populations at high risk for premature death, disease, and disability. During FY 1989 the DNRC and several institute members of the NCC participated on the NIH Task Force on the Nutrition Priority Area Year 2000 Health Objectives for the Nation and were extensively involved in writing and reviewing the nutrition priority objectives (see appendix H). The DNRC and FDA served as co-leads on the DHHS Task Force.

Collaborative Interagency Activities at the Federal Level

Interagency Committee on Human Nutrition Research - ICHNR

Chairs:	Assistant Secretary for Health, DHHS Assistant Secretary for Science and Education, USDA
Executive Secretariat:	NIH (DNRC)
Members:	DHHS (NIH, FDA), USDA (ARS, HNIS), NSF, AID, VA, NASA, OSTP, DOD, DOC

The ICHNR was established to improve coordination and increase the effectiveness and productivity of Federal agencies engaged in nutrition research. The committee is concerned with all federally supported or conducted research on nutrition with emphasis on human nutrition and professional personnel needs in nutrition research. The committee also coordinates the collection, compilation, and dissemination of information on nutrition research, including the Human Nutrition Research Information Management (HNRIM) System. The DNRC represents NIH on the ICHNR and has served as executive secretariat to the ICHNR since 1986.

The ICHNR has four subcommittees that carry out specific activities:

- Subcommittee on Research and the RDAs: identifies scientific issues that are of special relevance for the setting of dietary allowances.
- Subcommittee on Technology, Nutrition, and Food Production: monitors scientific, regulatory, and marketing developments with implications for the food supply.
- Subcommittee on Nutrition Monitoring Research: formulates an agenda of research tasks to improve capabilities in nutrition monitoring and interface with the Interagency Committee on Nutrition Monitoring.
- Subcommittee on the HNRIM System: reviews the classification system and codes, and contents of the data base.

In addition, the ICHNR organizes and sponsors the Biennial Conference for Federally Supported Human Nutrition Research Units and Centers. This meeting serves as a forum for information exchange and a stimulus for research collaboration among agencies. The fourth conference was held February 15-16, 1989, and addressed two topics of special interest to Federal nutrition researchers: "Nutrient Function" and "Nutrient Interactions and Toxicities." The ICHNR planning committee is now organizing the fifth conference, to be held in 1991. The topics to be addressed are "Studies on Dietary Risk Factors," "Minerals and Trace Elements—

Requirements and Safe Levels for Humans," and "Energy Balance, Body Composition, and Obesity."

Fish Oil Test Materials Program - FOTMP

Fish Oil Test Materials Advisory Committee	
Chairs:	NIH (DNRC), ADAMHA (NIAAA)
Members:	NIH (NCI, NHLBI, NIDDK), ADAMHA (NIAAA), DOC (NMFS/NOAA), FDA (CFSAN), extramural scientists

This program was formally initiated in 1986 by the signing of a memorandum of understanding (MOU) among the NIH, ADAMHA, and the DOC/NOAA. Under the MOU, the agencies agreed to cooperate on and provide support to research activities related to establishing and clarifying the biological mechanisms by which a seafood diet or the ingestion of fish oils, including omega-3 (n-3) fatty acids, may influence health and modulate a number of human disease processes. The program is administered through the DNRC by the Fish Oil Test Materials Advisory Committee (FOTMAC).

The purpose of the FOTMP is to provide a consistent supply of quality-assured/quality-controlled test materials to researchers in order to encourage high-quality research and to facilitate the evaluation of the role that omega-3 fatty acids have in human health and disease. To fulfill this purpose, during the summer of 1987, NOAA completed construction of a pilot plant in Charleston, South Carolina, which is now producing fish oil test materials including n-3 ethyl ester concentrate, ethyl esters of olive oil, purified eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), encapsulated purified steam-deodorized menhaden oil with and without antioxidants, and antioxidant-balanced control oils. To qualify to receive these quality-controlled test materials, researchers must have peer-reviewed research indicating the need for the

requested materials and submit a completed application form and a signed waiver of liability. Notices of availability of fish oil test materials are periodically announced in the "NIH Guide for Contracts and Grants" (see appendix I).

Human Nutrition Research Information Management (HNRIM) System

Contributing Agencies:	DHHS (NIH, FDA, ADAMHA, HRSA, NCHS, CDC), USDA, VA, AID, DOD, DOC, NASA, NSF
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The HNRIM System is a unique computerized data base and data retrieval system that contains information on all nutrition research and research training supported by the Federal government. Now in its eighth year of operation, the system is updated and maintained by the DNRC, under the auspices of the ICHNR.

Participating departments include DHHS, USDA, VA, AID, DOD, DOC, NASA, and NSF. The data base contains information on approximately 4,000 projects, with more than 2,400 supported by NIH. The 17 ICDs at NIH that support nutrition research annually provide data for the system. For each research project, the following information is included: name, institution, and address of the principal investigator; sponsoring Federal agency; project number assigned by the agency; title; abstract, if available from the sponsoring agency; total fiscal year expenditures, proportion that is nutrition related, and estimated nutrition expenditures; and nutrition classification codes. Appendix J contains the nutrition classification codes used in the HNRIM System.

Computer readable copies of the HNRIM System data are available for purchase by the general public through the National Technical Information Service, DOC. The data base also is accessible to the public through Dialog Information Retrieval Service, as a subfile of USDA's CRIS data base.

*Interagency Committee on Nutrition
Monitoring - ICNM*

Chairs:	Assistant Secretary for Health, DHHS Assistant Secretary for Food and Consumer Services, USDA
Members:	DHHS (NIH/DNRC, FDA, CCDPHP, NCHS), USDA (HNIS, ARS, FNS, ERS), AID, Bureau of the Census, Bureau of Labor Statistics, DOD, VA

The ICNM was formed in 1988 to improve the planning, coordination, and communication among agencies engaged in nutrition monitoring. As such, the committee monitors the overall effectiveness and productivity of nutrition monitoring efforts of the National Nutrition Monitoring System (NNMS), which includes all federally supported or conducted surveys on human nutrition and food consumption and surveillance of the food supply. To achieve these goals, the ICNM has three working groups:

- Survey Complementarity. This group aids the committee in working towards the integration of existing Federal surveys and surveillance activities into a network to provide a better overall view of both total population and special subgroups nutritional health.
- Federal-State Relations and Information Dissemination and Exchange. This group assists the committee in improving information exchange between nutrition monitoring data users and data generators, with a special focus on federal and state relations.
- Food Composition Data. This group monitors the availability and quality of food composition data for use in the NNMS and identifies food composition data needed. It also proposes improvements to data to facilitate coordination among member agencies.

The second progress report on nutrition monitoring in the United States was published

and submitted to Congress in 1989. It updates the dietary and nutritional status information presented in the 1986 report and provides an in-depth analysis of the contributions of the NNMS to the evaluation of the relationship of dietary and nutritional factors to cardiovascular disease and to the assessment of iron nutriture. For this report, the DNRC participated with other representatives from DHHS and USDA agencies in the Joint Project Steering Committee initiated in 1987.

In 1989 the ICNM produced its first publication, *Nutrition Monitoring in the United States: The Directory of Federal Nutrition Monitoring Activities* (DHHS Publication No.[PHS] 89-1255-1). The directory is a descriptive summary of current nutrition monitoring activities sponsored by Federal agencies, which includes various NIH surveys. It serves as a companion publication to the triennial reports to Congress on nutrition monitoring in the United States.

*USDA/DHHS Nutrition Education Committee
for Maternal and Child Nutrition Publications*

Chairs:	DHHS (HRSA), USDA (FNS)
Members:	DHHS: NIH (DNRC), HRSA, IHS, OHDS USDA: FNS, HNIS, ES, NAL

This committee provides a systematic mechanism for the USDA and DHHS to exchange information on progress and plans related to efforts in maternal and child nutrition education. The committee reviews publications to assure consistency of content, stimulates greater collaboration on joint projects, and increases dissemination of information on nutrition education. The DNRC represents the NIH on this committee.

During FY 1989, committee members collaborated on several major activities which required the joint expertise of both departments:

- Development of *Nutrition Management of the Pregnant Adolescent: A Professional Reference Guide*

- Development of recipes for commodity foods distributed on Indian reservations
- Publication and dissemination of *Nutrition Education Resource Guide for American Indians and Alaska Natives* for the Food Distribution Program on Indian Reservations

For additional information on the DNRC and NCC activities, contact:

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Section 2. Annual Reports of Institutes, Centers, and Divisions



NATIONAL CANCER INSTITUTE

Cancer is the second leading cause of death in the United States with more than 475,000 persons in 1987 dying from this disease. In the same period, more than 900,000 new cases of cancer occurred.

Since the NCI was established in 1937, scientists have identified various cancer-causing factors in the environment, and research leaders have sought to reduce the exposure of the population to those risk elements. Research and training at NCI are carried out by both intramural and extramural programs of the Division of Cancer Prevention and Control, the Division of Cancer Treatment, the Division of Cancer Etiology, and the Division of Cancer Biology, Diagnosis, and Centers.

Since the establishment of the Cancer Prevention Research Program (CPRP) by the Division of Cancer Prevention and Control in 1982, a coherent cancer prevention research plan, focused on nutrition, has been developed. This program has both intramural and extramural components which, when interacting with other NCI divisions and programs, allow prevention strategies to flow efficiently from the laboratory to the clinic. The intramural components of the CPRP are the Cancer Prevention Studies Branch and the Cancer Nutrition Laboratory; the extramural components are the Chemoprevention Branch, the Diet and Cancer Branch, and the new Cancer Prevention Clinical Trials Branch.

PROGRAM HIGHLIGHTS

NCI nutrition research is conducted with a variety of approaches: through epidemiologic studies of various population groups with distinctive food preparation and consumption patterns, by case-control and cohort studies, by clinical evaluations of dietary interventions, in laboratory studies of food content and components, and with biochemical/physiologic assessment of nutrient metabolism and absorption patterns in animals and humans. A number of epidemiologic and experimental

studies suggest that about 35 percent of cancer deaths may be related to dietary factors. Protection against certain types of cancer may be related, for example, to certain micronutrients such as vitamins C, E, and folate, trace minerals such as selenium, or perhaps certain carotenoids such as beta-carotene. A number of epidemiologic studies and clinical trials are now under way to determine the potential role of these agents in reducing cancer risk.

Diets high in total fat are associated with cancers of the breast, colon, uterus (endometrium), prostate, and ovary. High intake of foods rich in dietary fiber, on the other hand, may be associated with a reduced risk of colorectal cancer.

The CPRP in the Division of Cancer Prevention and Control seeks to identify ways to reduce the incidence or progression of cancer through applied intramural and extramural research in the areas of diet and nutrition and through chemoprevention. Research efforts in diet and nutrition focus on identifying dietary factors that inhibit the initiation or promotion of cancer. Studies and activities related to these factors include investigations of the metabolism of nutrients; the role of various nutrients and dietary components in causing and preventing cancer; the interaction of genetics, nutrition, and environment in the initiation or progression of cancer; the nutrient analysis of foods; the identification of determinants of dietary practices and development of methods to modify dietary practices; and the testing of hypotheses in dietary intervention clinical trials.

In 1988, a new intramural Laboratory for Nutrition and Cancer Research was established by the Division at the Frederick Cancer Research Facility in Frederick, Maryland. This intramural nutrition laboratory will focus on three major cancer prevention areas: basic nutrition research, nutritional epidemiology, and clinical/metabolic nutrition research. In addition, facilities have been identified at the

NIH Clinical Center for conducting body composition and nutrient metabolism studies and for controlled feeding studies.

Today, chemoprevention of cancer occupies a key position as a research strategy both at the NCI and among the many collaborating institutions throughout the world. To discover new innovative chemoprevention approaches, each year the NCI selects synthetic or natural micronutrients and other low molecular weight substances to be assessed either by investigations using experimental animals or through epidemiologic studies or clinical evaluation.

The nutrition program in the Division of Cancer Treatment (DCT) deals mainly with nutritional problems, including cancer cachexia, or wasting, which may arise in the course of chemotherapy. Poor prognosis of cancer patients often is associated with altered nutritional status. Anorexia, another symptom of cancer patients, may interfere with both the treatment and the patient's sense of comfort. Studies on the process of learned food aversions and possible remedies in a population of cancer patients receiving chemotherapy are ongoing. Promising therapies are tested to aid in stabilizing the weight of cancer patients. Metabolic abnormalities in malnourished patients and the effect of enteral feeding also are being investigated. The rationale for this hypothesis is that weight loss is due in part to an increase in total daily energy expenditure as a result of inefficient utilization of absorbed nutrients. Metabolic changes in cancer patients that provoke neurochemical and biochemical events causing cancer cachexia are being studied to provide new information on how these events may be modified. One group of investigators is examining the effect of total parenteral nutrition (TPN) on tumor growth and polyamine metabolism. They have found that L-ornithine reduces host toxicity of difluoromethyl-ornithine (DFMO) while not altering DFMO antitumor activity. Also, reduction of arginine and addition of ornithine to TPN solutions reduces tumor growth.

In other DCT research, investigators are continuing work on tumor necrosis factor (TNF) as a mediator of cancer cachexia. Most recently, researchers have shown that host macrophages are activated to produce TNF prior to the development of cachexia. As tumor burden increases, macrophage TNF production increases with concomitant tumor necrosis and cachexia. In addition, these researchers have shown that chronic TNF dosing can tolerize animals to TNF-induced cachexia; the effects can be reversed by insulin or antibodies to gamma interferon; and intermittent dosing of TNF leads to tolerance, whereas constant infusion does not.

Epidemiologic and experimental studies in the Division of Cancer Etiology continue to provide evidence that dietary factors contribute to a substantial proportion of human cancer. Variations among countries in cancer incidence and mortality rates suggest a significant role for dietary and nutritional factors; similar indications arise from migrant populations whose cancer rates, with increasing acculturation, resemble those of native-born groups. An increasing number of case-control and cohort studies have found certain dietary patterns to be associated with specific cancers. Nonetheless, many dietary factors remain to be investigated, and the nutritional etiology of most cancers is yet to be resolved. Efforts to generate and test hypotheses in this area continue to be emphasized in the division's intramural and extramural research program.

A large number of case-control and cohort studies are under way to examine the relationship of dietary patterns, specific foods, food groups, or nutrients to the incidence of cancer. Studies are being conducted in the United States and other countries to explore the effects of affluent diets, high in fat and calories, on the incidence of breast, prostate, colon, endometrial, and ovarian cancer, and the effects of diets low in vegetables and fruits on the incidence of lung, oral-pharyngeal, esophageal, colorectal, and cervical cancer. The relationship between alcohol consumption

and breast, oral-pharyngeal, and esophageal cancer also is being evaluated.

The Division of Cancer Biology, Diagnosis, and Centers funds research which explores how dietary components affect tumor cell growth and metastasis. Currently under way are projects to determine if saturated, mono-unsaturated, and polyunsaturated fats differ in their ability to stimulate growth of mammary tumor cells; to ascertain why some leukemia cells require only trace quantities of folic acid; to define the role of folic acid metabolism in the resistance of tumor cells to the chemotherapeutic agent, methotrexate; to purify a factor secreted by prostate and melanoma cells that stimulates the severe loss of stored fats associated with cachexia; and to understand why colon cancer cells cannot take up LDL-cholesterol via cell surface LDL receptors. Research continues in refining an *in vivo* murine nutritional model to study the effects of various essential fatty acids on growth and metastasis of colon cancer.

The Cancer Centers support a wide range of nutrition research projects including studies of dietary intervention in the prevention or treatment of cancer and vitamins and their relation to specific types of cancer. Other more basic studies are designed to examine the effects of nutrients on cellular metabolism, or to monitor tumor status in animals during nutritional treatment or deprivation.

The NCI also supports the continued upgrade and development of nutrition curriculum for medical students. Programs have been developed on the role of nutrition and diet in cancer etiology and prevention. In addition, pre-clerkship lectures, the expansion of clinical electives, and additional opportunities in basic nutrition research electives have been developed. In December 1988, the NCI provided support for a conference on "Nutrition and Cancer Education Objectives" held by the American Association for Cancer Education. Workshops were held on "The Nutrition and the Biology of Cancer," "Nutrition, Clinical Diagnosis, and Patient Management," and

"Nutrition and Cancer Prevention Education for Patients and the Public."

RESEARCH DIRECTIONS

The NCI is giving substantial emphasis to nutrition in its programs to reduce mortality from cancer. The NCI supports extensive research on the relationship between nutrition and cancer in a wide variety of areas: prevention, epidemiology, etiology, basic cellular mechanisms, therapy, rehabilitation, research development, and information dissemination.

Among the many research approaches being pursued, the following are of particular note:

- Through epidemiological investigations, assessments are being made about the effects of diet and nutritional status on cancer incidence and survival. Dietary factors under investigation include food groups (e.g., vegetables and fruit), specific foods (e.g., coffee), cooking practices (e.g., frying at high temperatures), and individual dietary constituents (e.g., beta-carotene, vitamin C, folate, fat, and dietary fiber). Nutritional parameters under investigation include plasma cholesterol, serum fatty acid profiles, fecal bile acids, and serum micronutrient levels. Studies are being conducted in low-risk populations, such as Chinese and Japanese migrants to the United States who have low rates of breast cancer, and in high-risk populations such as blacks who have high rates of prostate, pancreatic, lung, cervical, and esophageal cancers and multiple myeloma.
- Through chemoprevention and dietary clinical trials, studies are being carried out on the quantitative relationships between food, nutrient intake, and cancer incidence.
- Nutritive and non-nutritive dietary components are being assessed for their role in carcinogen metabolism.

- Investigators are studying mechanisms by which nutrients affect *in vitro* tumor cell metabolism and growth, including the role of folic acid in protein synthesis, the regulation of gene transcription by retinoids, the role of vitamin D₃ in inhibiting cell proliferation, the effect of essential fatty acids on colon tumor cell growth and metastasis, and the means by which chemotherapeutic agents alter cholesterol synthesis and cell membrane function.
- Methods of food preparation and processing, as well as ingestion of food and alcohol, fat, and fiber, are being appraised for their role in the promotion of cancer.
- Investigators are developing ways of measuring phytochemicals in fruits and vegetables and biological fluids, and assessing phytochemicals for their potential role in cancer prevention.
- The correlation between levels of micronutrients associated with cancer risk in blood and tissues is being evaluated.
- An international food component data base is being developed to enhance the quality, quantity, and worldwide accessibility of nutrient and non-nutrient data for research.
- The potential role of obesity, exercise, and immune dysfunction in cancer risk is being explored through both epidemiologic and laboratory studies.
- Researchers are seeking nutritional agents that may serve in the chemoprevention of cancer and are developing methodologies to evaluate the cost-effectiveness of these prevention strategies.
- Accurate and reliable means of measuring human dietary intake are being developed.
- Improved methods for assessing nutritional status, metabolic patterns, and genetic predisposition are being evaluated for use in epidemiological studies.

Clinical aspects of the care and management of cancer patients require focused nutrition

research, not on cancer prevention, but on the effective treatment of cancer. Among such investigative studies are the following:

- Clinical trials are under way to evaluate the effectiveness of nutritional support in the rehabilitation of the cancer patient, nutrition requirements during remission, and nutrient and dietary factors needed to maximize patient survival.
- The nutritional requirements of the cancer patient and neoplastic tissues are being appraised, with emphasis on nutrient uptake, utilization, and cellular control mechanisms in both normal and neoplastic tissues, and on host-tumor interactions and competition for nutrients. This research helps to develop a more complete understanding of tumor growth and differentiation as it affects the host's metabolism. Knowledge of growth requirements and control mechanisms helps to formulate new therapy schemes based on differential nutrient availability.
- In order to develop techniques and procedures to maintain or improve the nutritional status of the patient, various formulations and delivery systems in total parenteral and enteral nutrition and oral supplementation are being examined. Energy expenditures also are being measured using whole body calorimetry. Behavior modification procedures and pharmacological agents are used to improve the appetite of cancer patients. In addition, laboratory research is under way on the etiology of cachexia, or wasting, in cancer patients.
- Three Clinical Nutrition Research Units, each conducting an intensive program of nutrition research, are funded through the NCI.
- Educational materials and programs are being developed on the role of diet and nutrition in cancer etiology, prevention, treatment, and rehabilitation for dissemination to health care professionals and to the public.
- Investigators are studying mechanisms

by which nutrients affect tumor cell metabolism and growth, including the accumulation of intracellular metabolites and alterations in glucose production in cancer cachexia; the effect of total parenteral nutrition on tumor growth and polyamine metabolism; the nutritional effects of nucleotides on lymphocyte function; and regulation of glutamine metabolism through high glutamine diets and tumor metabolism.

- A clinical study is under way to examine the effect of megestrol acetate on weight gain in stage III non-small cell lung cancer patients. Three possible mechanisms will be studied: increased food intake, decreased energy expenditure, and fluid retention.
- The cooperative groups are studying the effects of therapeutic interventions affecting nutrition in several randomized trials. The Cancer and Leukemia Group B (CALGB) is randomizing breast cancer patients to three different doses of a synthetic progestin (Megace). The same cooperative group is randomizing patients having metastatic non-small cell lung cancer to chemotherapy (cisplatin + VP-16) with or without hydrazine sulfate, a presumed anti-cachexia agent which interferes with "spurious gluconeogenesis." The North Central Cancer Treatment Group (NCCTG) is conducting a similar study in the same patient population. Finally the NCCTG is randomizing extensive stage small cell lung cancer patients to chemotherapy (cisplatin + VP-16) with or without Megace.

efficacy of an intervention for human populations. Multi-institution trials are often necessary to achieve an adequate number of trial participants. The new Cancer Prevention Clinical Trials Branch will stimulate and facilitate these trials.

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OUTLOOK

Research leaders have concluded that controlled intervention trials, when feasible, represent an integral part of the effective bridge between basic knowledge and the application of research results to cancer prevention. Although costly and often complex, well-designed randomized, controlled trials can provide the most definitive evidence of the

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

The NHLBI provides leadership for a national program in diseases of the heart, blood vessels, lungs, and blood, and in the uses of blood and in the management of blood resources. Through its intramural and extramural programs, the NHLBI conducts and supports an integrated research program that includes basic research, clinical trials, epidemiologic, and demonstration and education projects that relate to the causes, diagnosis, treatment, and prevention of heart, blood vessel, lung, and blood diseases. In addition, the NHLBI supports research training of new investigators and the career development of established researchers in both basic and clinical research related to heart, blood vessel, lung, and blood diseases and transfusion medicine.

The diseases within the purview of the NHLBI impose a heavy burden on the health and economy of the American people.

Cardiovascular, lung, and blood diseases accounted for 1,159,000 deaths in 1987 or 54 percent of all deaths. They represent 5 of the 10 leading causes of death, 6 of the 10 leading causes of infant death, and 5 of the 13 leading chronic conditions that result in varying degrees of limitations of activity.

Cardiovascular diseases alone were responsible for approximately 46 percent of all deaths in 1987.

In 1986, the economic costs of diseases of the heart, blood vessels, lungs, and blood was nearly \$165 billion in economic costs, or nearly 24 percent of the total economic costs of all illnesses and premature deaths. This cost estimate represents \$75.5 billion in direct health care expenditures, \$31.3 billion in indirect costs of lost productivity due to illness, and \$58 billion in indirect costs that result from lost productivity due to premature death.

The search for new knowledge about disease processes and improved methods of diagnosis and treatment has led to important advances against heart, blood vessel, lung, and blood diseases. The overall improvement in mortality from cardiovascular diseases is

reflected in the rapid increase in life expectancy in recent years. The downward trend in mortality from these diseases has persisted over the last 20 years, and the impact of the decline has been substantial. The age-adjusted rate for all causes of death dropped from 726 deaths per 100,000 in 1967 to 536 per 100,000 in 1987, and 79 percent of the reduction is due to the decline in the death rate from cardiovascular diseases.

The programs of the institute have several dimensions. The combination of fundamental research, population based studies, behavior research, and clinical trials is designed to provide a comprehensive approach to developing an understanding of the causes of cardiovascular, lung, and blood diseases, to assist in their diagnosis, and to develop strategies to reduce the related morbidity and mortality.

After new information has been acquired and health care strategies have been validated, the information is ready for transfer to physicians, other health care personnel, and the general public. Educational and informational materials discuss clinical applications of research results in addition to scientific and technical information about heart, blood vessel, lung, and blood diseases. The National High Blood Pressure Education Program, the National Cholesterol Education Program, the NHLBI Smoking Education Program, the National Blood Resource Education Program, and the new National Asthma Education Program are major ongoing education efforts and are designed to provide information about these areas to health care practitioners, patients, and the public.

The institute's overall objective in integrating basic and clinical research and disseminating information about health care strategies is to reduce the morbidity and mortality of heart, lung, and blood diseases in the United States. The NHLBI's research and training program is administered through a variety of funding mechanisms. In its nutrition program as in other NHLBI research, the Institute's research

efforts are focused in four extramural divisions: the Division of Heart and Vascular Diseases, the Division of Lung Diseases, the Division of Blood Diseases and Resources, and the Division of Epidemiology and Clinical Applications. Additional studies are conducted in the Intramural Division. The Office of Prevention, Education and Control is responsible for the development and dissemination of nutrition information and materials related to the risk factors for cardiovascular heart disease.

PROGRAM HIGHLIGHTS

To carry out its research goals, the NHLBI conducts its nutrition research across a broad spectrum, from biochemical studies of the cell and its DNA to clinical studies of dietary interventions aimed at reducing the risk of disease-related morbidity and fatality. Applied research, demonstration projects, public education, and research training programs are under way with the ultimate goal of improving the nutrition and health of the U.S. public.

Nutrition and Cardiovascular Health

Three NHLBI research programs are studying cardiovascular risk factors in children ages 8 years and up. One study focusing on children with elevated levels of LDL cholesterol is a randomized clinical trial called DISC (Dietary Intervention Study in Children). Following the successful completion of a feasibility phase which studied 146 children, ages 8-10 years at entry, the study proceeded with the full-scale trial. The trial has randomized 677 children (113% of goal) and their families to test the long-term efficacy, acceptability, and safety of a fat-modified diet designed to lower blood LDL-cholesterol levels in children. The children will be followed for at least 3 years.

Another study, the National Growth and Health Study (NGHS), is a 5-year observational study on 2,000 girls ages 9-10 years. Its purpose is to investigate racial differences in the onset and occurrence of obesity and other cardiovascular risk factors in black and white girls.

Finally, a multicenter, collaborative field trial called Child and Adolescent Trial for Cardiovascular Health (CATCH) is completing a feasibility study involving over 1,400 elementary school children at study sites in California, Louisiana, Minnesota, and Texas. The main trial will be conducted from 1991-1994 and will enroll 12,000 students of diverse racial, ethnic, and socioeconomic backgrounds. They will participate in the study during the third through fifth grades.

The overall goal of CATCH is to assess the effect of a school-based intervention for promoting healthful behavior in elementary school children to reduce their subsequent cardiovascular disease risk. The interventions include components of classroom curricula, family education, and school environmental modifications related to school lunch, physical activity, and tobacco use. These interventions are aimed at improved physical activity levels, nonuse of tobacco, a lower level of total fat and sodium consumption, and increased consumption of complex carbohydrates. These behavioral changes are expected to favorably influence serum lipids and lipoproteins, physical fitness, and blood pressure. The interventions are based on behavioral research and social learning theory and have linkages across the intervention components including curriculum, environment, and family. Behavioral and physiological measures will be the means for testing the effectiveness of the school and family-based interventions.

Several NHLBI cardiovascular risk reduction research programs are under way on adults as well. These clinical studies are testing prevention and intervention strategies, many of which have nutritional components for preventing and treating hypertension.

International Cardiovascular Nutrition Research

Since 1981, U.S. and Chinese scientists have collaborated on large-scale epidemiological studies, jointly supported by the NHLBI and the PRC ministry of health, that compare trends, rates, and risk factors for

cardiopulmonary disease. The investigators are studying more than 11,000 workers from 4 populations in Beijing and Guangzhou. A baseline survey was completed in 1986. Participants were rescreened in 1987. When the phase II data were compared with the phase I data the researchers found that all Guangzhou population subgroups had significantly increased their mean serum levels of total cholesterol, LDL-cholesterol, and triglycerides during the interim period. These results suggest an unfavorable lifestyle trend in the Guangzhou area. Similar trend analyses must be completed for data from North China before investigators can determine whether a similar shift in blood lipids has occurred among the study's Beijing participants. Based on the unfavorable risk factors profile of Beijing workers, intervention studies are being carried out to reduce smoking, salt intake, and elevated blood lipids, high blood pressure, and obesity in certain groups of workers.

Joint scientific research agreements between the NHLBI and the U.S.S.R. since the early seventies has allowed for collaborations in nutrition research areas which have centered on epidemiologic studies of cardiovascular disease risk factors, morbidity and mortality. Basic and clinical research on the effects of lipoproteins on atherosclerosis and joint hypertension studies between the two countries has allowed for better understanding and control of these disorders. In addition, joint research in the area of cardiopulmonary epidemiology and prevention continue, collaborating on epidemiology studies of primary prevention of hypertension in children and health education in the United States and U.S.S.R. on areas such as hypertension and cholesterol.

These studies, because of the differences in the prevalence of risk factors and rates of disease among three countries, are providing new insights in our understanding of the causes and sequela of coronary heart disease (CHD).

The National High Blood Pressure Education Program

Lifestyle and behavior changes have been the cornerstone of the NHBPEP. In FY 1989, a series of working group reports, editorials, and position papers were developed to set program and national guidelines for the management of hypertension. These reports will be published in professional journals and the information contained in them will be included in new materials prepared by the NHBPEP. During FY 1989, a national conference on high blood pressure control, cosponsored by the International Interdisciplinary Conference on Hypertension in Blacks, was held in Orlando, Florida. The conference attracted approximately 700 participants to focus on hypertension in special populations. The first Sunday in May was declared Church High Blood Pressure Sunday, and this event was celebrated at the national conference. The Fourth Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC IV) was reprinted—200,000 copies of these guidelines for physicians have already been distributed to primary care physicians. A set of slides based on the report also was made available to help others make presentations on the guidelines. In the fall and spring, the high blood pressure radio and television public service announcement campaigns were released that were designed to encourage hypertensives to remain on their pharmacologic and nonpharmacologic treatments, such as therapies of weight loss and salt restriction and avoidance of alcohol.

The National Cholesterol Education Program

Since its inception in 1985, the NCEP has made substantial contributions to the successful nationwide campaign to raise professional and public awareness about the importance of

lowering high blood cholesterol levels. In the area of improving the management of high blood cholesterol, the NCEP conducted a series of activities to extend the influence of the Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel) guidelines and to expand the high risk strategy from its current focus upon adults. An Expert Panel on Blood Cholesterol Levels in Children and Adolescents was formed. A continuing medical education module, updated to reflect the Adult Treatment Panel guidelines, was provided to such groups as the Alliance for Continuing Medical Education, medical schools, the American Medical Association, the National Medical Association, and health maintenance organizations. Over 1,500 professionals participated in the first National Cholesterol Conference, held in November 1988. Patient education brochures were reprinted and widely distributed. The NCEP also implemented activities to improve the public's understanding of high blood cholesterol and promote healthful eating patterns. The Expert Panel on Population Strategies for Lowering Blood Cholesterol Levels has examined the scientific evidence upon which recommendations have been made for a population approach to lower the mean blood cholesterol level by modifying the dietary habits of the entire population. A new mass media campaign was developed, which encouraged the public to get their cholesterol checked and to take appropriate steps if their levels are high. The first annual National Cholesterol Education Month took place in September 1989. The second is planned for September 1990.

During FY 1989, a focused outreach was directed toward dietitians. A "Dietitian's Kit" was developed in cooperation with the American Dietetic Association (ADA) and the American Heart Association (AHA). Key components of the kit include copies of patient education brochures (*Eating to Lower Your High Blood Cholesterol, So You Have High Blood Cholesterol*, and a fact sheet on blood cholesterol), the Adult Treatment Panel guidelines, a continuing education article

published in the *Journal of the American Dietetic Association*, a poster on step I and II diets, a community guide to cholesterol resources, and order forms for additional NHLBI, AHA, and ADA materials. This outreach initiative also includes training for dietitians on the Adult Treatment Panel guidelines at nine Skills Development Workshops sponsored by the ADA. All workshop participants received the Dietitian's Kit of program materials. The kit also was presented to all ADA members at their annual meeting in October 1989.

In addition, a nursing education program has been developed. The program is cosponsored by the NHLBI, the AHA, the American Nurses Association, the National Black Nurses Association, and the National Center for Nursing Research. Its objective is to educate registered nurses about identification, treatment, and management of patients with elevated blood cholesterol.

Another example of a successful FY 1989 program is "Play Your Cards Right...Stay Young at Heart," a nutrition education point of purchase program initially introduced at NIH cafeterias during NHLBI month of the NIH Centennial Celebration in 1987. The program involved the use of 11 recipes that originated in the Multiple Risk Factor Intervention Trial and Coronary Primary Prevention Trial which are lower in saturated fat, cholesterol and sodium, and various other useful materials (recipe cards, dispenser, apron, button, poster, tent card, evaluation card, and flyer). Because of its success at the NIH cafeterias, the program has been implemented in 22 states in a variety of settings. The program was repeated at NIH in March 1989 for National Nutrition Month. Another 14 recipes and a new poster to be featured at the NIH during National Cholesterol Education Month, in September 1990, currently are being developed.

Due to the interest in the program, a kit was developed that contains the aforementioned materials along with a background paper on the NHLBI program, implementation, a public information fact sheet, quantity recipes, and

reproduction guidelines. Many organizations have requested the kit in order to implement the program in a variety of settings.

RESEARCH DIRECTIONS

In its nutrition program as in other NHLBI research, the institute's prevention efforts are targeted toward heart and vascular diseases, lung diseases, and blood diseases and resources. The following are examples of research supported by the NHLBI:

Heart and Vascular Diseases

- Identify mechanisms by which nutrients and other dietary factors influence blood pressure both under normal conditions and with hypertension.
- Explore the role of nutrition in intervention studies of cardiovascular disease risk.
- Conduct studies to determine racial, ethnic, and female differences in CHD including metabolism, risk factors, and diet responsiveness.
- Identify behavioral determinants of food consumption patterns and nutrient intake in relation to the risk of disease and the promotion of health.
- Improve the measurement of diet and nutrient intake, including acquisition of food composition data and development of automated methods of assessing dietary intake of individuals.
- Develop effective nutrition education strategies, methods, and materials for the dissemination of information on nutrition and disease prevention to health professionals and to the public in schools, work sites, clinics, and communities.
- Support training in nutrition as it relates to heart and vascular diseases.
- Elucidate the role of body weight and diet in cardiovascular disease and its risk factors.
- Continue surveillance of public knowledge and physician practices that pertain to diet and cardiovascular disease.

Lung Diseases

- Improve the understanding of the effects of nutritional status on immune defense

functions in the developing and adult lung; the effects of malnutrition on normal resistance to pulmonary infections; and the role of nutritional factors in the development of bronchopulmonary dysplasia.

- Explore the role of nutrition in preventing respiratory muscle dysfunction in acute and chronic pulmonary disease.
- Support studies on the role of various nutrients on nonrespiratory lung functions such as the synthesis and metabolism of surfactant and prostaglandins.
- Determine the effect of dietary factors on the central control of breathing and on neurophysiology within the lung and airway tissues.
- Investigate the role of specific nutrients in adult and infant respiratory distress syndromes and in other forms of respiratory failure.
- Support training in nutrition as it relates to lung diseases.

Blood Diseases and Resources

- Identify mechanism(s) by which nutrients and other dietary factors influence the blood-clotting function of platelets.
- Elucidate the role of nutrients and other dietary factors in the genesis, treatment, and prevention of blood vessel obstruction.
- Continue research on energy balance and nutrient requirements among children with sickle cell disease, especially children who fail to thrive and adolescents who are in the rapid growth phase.
- Determine the time of appearance and the intensity of nutritional abnormalities in sickle cell patients.
- Conduct studies on the benefits of appropriate dietary intervention and nutritional supplementation on growth and development, and on the morbidity of children with sickle cell disease.
- Improve understanding of nutritional factors in the management and clinical variability of sickle cell anemia.
- Characterize the relationship of nutritional deficiencies and immune dysfunction in sickle cell disease.
- Support training in nutrition as it relates to blood diseases and resources.

- Elucidate the role of nutrients and other dietary factors on the genesis and treatment of high blood pressure.
- Support research in nutrition education for medical students and for physicians in their private practice.
- Continue to support research to improve assessment and control of diet in research studies.

OUTLOOK

The NHLBI seeks to meet its goals of better health for the American people through research leading to improved diagnosis, treatment, and prevention of heart, vascular, lung, and blood diseases. The institute's nutrition research program is a key element in this effort.

Surgeon General C. Everett Koop noted in his July 1988 *Surgeon General's Report on Nutrition and Health* that Americans are already making dietary changes, as witnessed by the shift to products lower in saturated fats. It is NHLBI's objective to extend the gains already made in national eating behaviors by applying research strategies and technology to nutrition, thereby reducing the premature death rate from cardiovascular, pulmonary, and blood diseases.

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NATIONAL INSTITUTE OF DENTAL RESEARCH

The NIDR is the primary sponsor of dental research and related training in the United States. Its mission is to support studies to establish the causes, to develop better treatments, and to find ways to prevent or substantially lower the risk of developing oral diseases and disorders.

Institute scientists, as well as those affiliated with grant-supported NIDR programs, have made encouraging progress in improving the nation's oral health through advances in diagnosis, treatment, and prevention. The Institute has organized its efforts into an Extramural Program (EP) and the Intramural Research Program (IRP) centered in NIDR's own laboratories and clinics in Bethesda. The NIDR added an Epidemiology and Oral Disease Prevention Program to the IRP in the mid-1980's. This program sponsors epidemiologic studies of oral diseases and disorders and engages in controlled clinical trials of potential preventive agents and regimens, promoting their dissemination to the dental profession and the general public.

PROGRAM HIGHLIGHTS

Impressive gains in oral health have been made which can be attributed to a variety of preventive measures, some as a result of an increased appreciation of the influence of diet and nutrition. The successes are not complete, however. Dental caries and periodontal diseases remain the most prominent, prevalent and costly oral health problems worldwide.

Role of Fluoride

The 1987 NIDR survey of U.S. school children ages 5-17 years showed a dramatic decrease in tooth decay with approximately one-half of the children being caries-free in their permanent teeth. However, 84 percent of all 17-year-olds surveyed had experienced tooth decay in their permanent teeth. Recent analysis of the survey findings indicates that children who always had been exposed to community water fluoridation had caries scores significantly lower than did those who had

never lived in fluoridated communities. The results indicate that water fluoridation plays an important role in the decline of caries and must continue to be a major prevention methodology.

Fluoride in toothpastes, mouth rinses, topical gels, prescription tablets, and food processed with fluoridated water is commonplace today. Mild tooth fluorosis has been observed in some children on clinical examination. Epidemiologic studies are being carried out to determine the prevalence of dental fluorosis. Scientists are testing fluoride in combination with other substances or vehicles in mouth rinses that increase the effectiveness of lower levels of fluoride in preventing tooth decay. Fluoride studies in animals are assessing its bioavailability, incorporation into hard tissues, and the effect of its interaction with minerals and other dietary components on its absorption and assimilation.

Adult Studies

Adult oral health fails to demonstrate a decline in dental decay prevalence similar to that seen in children. Although adults experience coronal caries, the major type in children, they also have caries on the exposed roots of teeth (root surface caries). Epidemiologists have identified associations between root caries and a variety of clinical, laboratory, dietary, and psychosocial factors. One study found that people who lived in nonfluoridated areas for 30 years or more had a greater risk of both coronal and root caries than did those living in fluoridated communities.

The NIDR "Research and Action Program for Improving the Oral Health of Older Americans and Other Adults at High Risk" aims to prevent tooth loss and further deterioration in oral health status among older generations of Americans. The problems of these groups were documented in the 1985-86 NIDR adult survey which showed that older Americans continue to experience coronal caries and have the highest rates of root surface caries and the most severe periodontal disease of any age group. In this

population, untreated dental decay, gingivitis, and more advanced periodontal diseases can be painful, interfere with chewing ability and speech, alter the choice and taste of foods, and affect general health. Research to study the dietary intake of older cohorts of Americans, the effects of oral health problems (such as toothlessness) on dietary choices, and the relation of systemic disease and medications to diet and oral health, are among the epidemiological and clinical studies relevant to the Research and Action Program. For example, clinical studies of periodontal diseases in older adults are characterizing the factors which discriminate among older Americans with and without periodontal destruction. One aspect of the studies is to collect food intake data in order to estimate percentage RDA for important nutrients and to determine if a relationship can be established between diet and/or nutrition and disease.

The Research and Action Program also is designed to spur the basic and clinical research necessary to drive nationwide public and private sector actions to improve the oral health of all Americans as well as to facilitate and encourage other organizations to expand their own activities. The NIDR's primary role will be to expand the knowledge base and accelerate the transfer of laboratory findings to the public and to the profession.

In FY 1989 the NIDR cosponsored with NIA and DNRC a workshop on Diet and Nutrition and the Maintenance of Oral Health in the Elderly.

Special Population Studies

The NIDR also emphasizes the need to identify for early prevention individuals at high risk for oral diseases. This will entail improving and modifying research methods and measurements to document the knowledge, attitudes, and behaviors of low-income, nutritionally deprived, low-education persons, and other groups at high risk for oral diseases. Epidemiologic, behavioral, and social science

research is essential to document the prevalence of oral diseases in special populations (e.g., the frail, the handicapped), identify risk factors, advance prevention research, and monitor science transfer.

The NIDR surveys of children and adolescents indicated that small subgroups of these younger populations have disproportionately high levels of dental caries. NIDR-supported research seeks to determine who among young people is at higher disease risk and why. From a nutritional standpoint, studies of dietary choices and habits of these children at high risk seek to determine if there is a background of malnutrition, undernutrition, or too frequent snacking of sugar-rich foods and to develop means of remediation, including appropriate diet and dietary habits, and the use of fluorides.

A major initiative in the new NIDR Long-Range Research Plan for the Nineties focuses on individuals whose oral health is compromised because of medical conditions (and their treatments) or because of physical or mental handicaps. Examples of these "special care" patients include individuals with diabetes who are at high risk for periodontal disease, people who daily take any one of several hundred medications that have the side effect of dry mouth (which deprives the oral tissues of the tissue-protecting and preserving components in saliva), cancer patients who receive chemotherapy or radiation to the head or neck, children with genetic or congenital diseases that affect tooth and bone formation (e.g., cleft lip/palate, osteogenesis imperfecta, ectodermal dysplasias), adults with autoimmune diseases such as Sjogren's syndrome, and the many patients whose neurological, psychiatric, or musculoskeletal problems preclude appropriate oral hygiene or impose barriers to dental care. A number of these conditions can affect appetite and eating habits either because they interfere with normal chewing and swallowing, or because of oral soreness due to ulcers or other lesions affecting the oral mucosa.

Minority Emphasis

The categories of individuals at risk as defined either by the Research and Action Program or the Special Care Patient Initiative include many from minority groups. In some cases this is because of higher prevalences of disease (e.g., diabetes among Native Americans and blacks), but often the reason is lower socioeconomic status and associated barriers to dental care. The NIDR Long-Range Research Plan calls for research that will document the oral health status of racial and ethnic minorities. This research ranges from epidemiological and risk factor analysis to the design of culturally sensitive prevention and treatment programs. Such research programs include analyses of dietary habits that may increase risk.

International Activity

NIDR continues to participate with the World Health Organization and other appropriate professional organizations in activities to promote and implement the initiative, International Collaboration for Oral Health Research. At a workshop in April 1989, sponsored by the Fogarty International Center and the NIDR in collaboration with the World Health Organization, dental scientists from around the world presented their research priorities for international collaborative oral health research in a range of scientific areas including nutrition. In March 1989 the NIDR supported the "International Symposium on Fluorides: Mechanisms of Action and Recommendations for Use." NIDR staff members now are working to implement the recommendations from these meetings. International collaborative studies involving extramural scientists and dental researchers in Mexico and in South America are determining the effects of malnutrition on tooth enamel formation, tooth eruption, and dental caries.

Nutritional Deficits and Oral Disease

Multiple nutrient deficiencies have been shown to increase the permeability of oral epithelia

in experimental animals. As a result, the animals' tissues appeared to become more vulnerable to periodontal diseases and soft tissue lesions, conditions analogous to those seen in human nutritional deficiencies.

Decreased salivary flow rate, directly or indirectly related to dietary intake, has been shown by NIDR-supported scientists to result in predictable patterns of increased dental caries and gum inflammation. Subclinical nutritional deficiencies of vitamin C and folic acid have been found to worsen periodontal problems, both in humans and in nonhuman primates. Other deficits, including lack of iron, folate, and vitamin B₁₂, have been linked to the development of aphthous inflammation of the oral mucous membranes.

RESEARCH DIRECTIONS

NIDR's nutritional research focuses on the relationship between diet and the development and maintenance of both hard and soft tissues of the oral-facial complex. Special interests are in the areas of tooth and gum development and maintenance, periodontal diseases, and dental caries, particularly as they are affected by nutritional factors. Examples of nutrition research supported by the NIDR are as follows:

- Studies on the effects of nutrients during embryonic life, particularly as they relate to oral structures, e.g., the role of nutrition in craniofacial malformations and developmental defects of cleft lip and palate.
- Investigations to determine the effects of poor nutrition on the fundamental integrity and metabolism of healthy oral mucous membranes, e.g., the effect of nutrition on salivary gland function, including the secretory immune mechanism.
- Research on the effects of nutrition on the biology of bone and soft tissue, the etiology and prevention of oral ulcerative diseases, and immune function.
- Research to define critical periods of development of oral tissues that may be sensitive to nutrient intake and the role of

nutritional factors in the maintenance and repair of the periodontium and oral tissues.

- Research on the role of nutrition and nutritional status in the etiology and pathogenesis of oral diseases in older persons and other high-risk populations.
- Research to define mechanisms underlying relationships between oral diseases or conditions and chemosensory disorders.
- Examination of the metabolic effects of various fluoride levels in humans, especially the effect of fluoride received prenatally, and investigation of dental fluorosis.
- Studies on the effects of zinc deficiency on the epithelium lining in some regions of the oral cavity.
- Investigation into the structure, nutritional requirements, and normal functioning of salivary components such as mucins (important in lubrication), histidine-rich proteins (with specific antifungal properties), and proline-rich proteins (important in remineralization of tooth enamel). Scientists also are studying salivary gland dysfunction, particularly as a result of cancer therapy.
- Research on the effect of dietary factors, such as vitamin A, vitamin E, and alcohol, on the initiation and progression of oral cancers.

OUTLOOK

The new Long-Range Research Plan for the Nineties reflects the major growth of oral health research and a commitment to address all the diseases and disorders that affect the orofacial tissues, "from AIDS to xerostomia (dry mouth)." Thus, in the special section on nutrition there are recommendations for research on the effects of dietary factors on specific diseases including caries, periodontal diseases, diabetes, osteoporosis, and oral cancer, in addition to research on nutrition in relation to the normal growth and development of the oral tissues. Nutrition research also figures importantly in two broad programmatic initiatives highlighted in the plan. These initiatives focus on individuals or groups at

high risk for oral health problems and the need to develop improved prevention and treatment approaches for them.

The NIDR will continue to foster collaborative efforts with other NIH institutes, centers, divisions, and government agencies in nutrition research and oral health.

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NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Since its creation in 1950, the NIDDK's research responsibilities have included nutrition-related programs to prevent and treat disorders such as liver and biliary diseases; pancreatic diseases; gastrointestinal, digestion, and absorption disorders; diabetes; obesity; a variety of endocrine disorders; kidney and urological diseases; metabolic diseases, including cystic fibrosis; and eating disorders. The NIDDK plays an important role in the study of nutritional factors relating to the etiology, prevention, and treatment of diabetes, digestive, and kidney diseases. This research is supported out of three divisions: the Division of Diabetes, Endocrinology, and Metabolic Diseases; the Division of Digestive Diseases and Nutrition; and the Division of Kidney, Urologic, and Hematologic Diseases.

More recently, an expansion of nutrition research training in the areas of nutrient metabolism, obesity, eating disorders, and energy regulation is being encouraged. In response to the fact that both applications and awards in research training have declined since the beginning of this decade, an annual request for applications (institutional training grants, individual postdoctoral fellowships, and career awards) has been initiated this year as a means to re-establish a strong nutrition research training base in the 1990's.

PROGRAM HIGHLIGHTS

Cytokines

Recently, a number of local growth factors, or cytokines, that may play a role in regulation of bone metabolism have been identified. These cell-derived factors are synthesized by leukocytes, fibroblasts, osteoblasts, and other cell types. The factors include bone-derived growth factors, cartilage-derived growth factor, human skeletal growth factor, human platelet-derived growth factor, human and transforming growth factors, epidermal growth factor, tumor necrosis factors, interleukins, interferon, and relaxin. Some of these factors are produced by normal cells and may regulate the normal processes of bone metabolism.

Others are produced by human or animal tumors and may mediate the pathological bone resorption and hypercalcemia associated with cancer. The possible role of these local growth factors in mediating the effects of systemic hormones remains to be determined.

Leukocyte endogenous mediator (LEM) has been implicated in the host's initiation of protein metabolic response to infection and inflammation. To determine whether administration of LEM would alter protein kinetics, appearance of oxidation of plasma tyrosine as well as the rates of protein synthesis in liver and skeletal muscle was determined. Results suggest that administration of LEM stimulates mobilization of amino acids from peripheral tissues to support increased visceral protein anabolism while whole body amino acid oxidation also is enhanced. Similar effects follow fever and infection, implying that LEM may play an underlying role in the protein metabolic response to infection and inflammation.

Metabolic alterations related to resting energy expenditure and fat metabolism have been noted during sepsis and often depend on the causative agent and the stage and severity of the illness. Studies have been conducted on the effect of interleukin 1 or IL-1, the protein mediator of the acute phase response during infection, on resting energy expenditure, respiratory quotient, and fat metabolism. From these investigations it was concluded that IL-1 can mimic the increase in resting energy expenditure seen during infection, and the increase in resting energy expenditure is not due to a selective increase in fat oxidation alone.

Fatty Acids

Recent studies have indicated that feeding animals a diet whose lipid source is fish oil will significantly improve survival following endotoxin exposure. Long term fish oil administration was shown to ameliorate the effect of endotoxin to produce systemic lactic acidosis. The significantly reduced serum lactate in fish oil fed animals with

normoxemia in all groups suggested that the underlying mechanism involved improvement in endotoxin-induced tissue hypoperfusion. Fish oil enriched diets also attenuated the catabolic effects induced by recombinant mediators as evidenced by reduced leucine oxidation. This reduction in net protein catabolism was not associated with a diminution in either breakdown rate or net breakdown in skeletal muscle. However, the observed increase in liver weight in the fish oil fed animals was felt to be reflective of an increase in visceral protein synthesis. These investigations have suggested that dietary fat can have a profound effect on the host's response to infection or other toxic insults.

The metabolism of individual dietary n-3 fatty acids was studied in n-3 fatty acid deficient newly hatched chicks. Retroconversion of dietary 22:6 to 22:5 and 20:5 was evident in serum, liver, and retina but not in the brain. Thus, it was possible to study the relative metabolism and especially the intraconversion of n-3 fatty acids in an environment uncomplicated by existing stores of these essential fatty acids. The studies suggested that 18:3 as a source of n-3 fatty acids in the diets of animals, including the human infant, may not be adequate for the biochemical development of the brain and retina and that dietary DHA (22:6 n-3) is the preferred fatty acid of the n-3 series.

The effects of a fish oil supplemented diet on infarct size and regional myocardial blood flow were examined in the rat model. Rats were fed a diet containing 20 percent by weight fish oil, corn oil, or beef tallow. Enrichment of membrane phospholipids with n-3 polyunsaturated fatty acids resulted in an increased postischemic myocardial blood flow in this ischemia-reperfusion model in the rat. Despite the enhanced postischemic blood flow, the fish oil supplemented group did not have a reduced infarct size.

Because red blood cells are rich in highly unsaturated lipids and are continuously exposed to a high oxygen concentration, they are highly

sensitive to oxidative damage. When insufficient dietary antioxidants are consumed, oxidative damage to polyunsaturated fatty acids will occur. Thus, testing the oxidative lability of the red blood cell membrane to peroxidation *in vitro* may assess the effects of prooxidant conditions in humans. Varying the polyunsaturated fatty acid content of the human diet did not result in acceleration of the rate of oxidative reactions in the red blood cell membrane. Under conditions of low *in vitro* oxidant challenge, the physiological antioxidant defenses were able to overcome the oxidative stress, but when exposed to greater oxidative stress, the antioxidant defenses were overwhelmed, and lipid peroxidation became dependent on the polyunsaturated substrate.

Supplementation with vitamin E was shown to lead to decreased susceptibility to *in vitro* lipid peroxidation in tissues from rats fed either a corn oil, lard, or menhaden oil diet at comparable polyunsaturated fatty acid levels. Vitamin E appears to be more effective when the lipid source was high in n-6 fatty acids than when n-3 fatty acids predominated. Enhanced susceptibility to lipid peroxidation was evident in tissues from rats fed a moderate level of fish oil.

Other investigators demonstrated that the protection against lipid peroxidation provided by a combination of antioxidants (dietary supplements of vitamin E, beta-carotene, and selenium) was either additive, less than additive, or synergistic. Therefore, the combination of dietary treatments and tests of tissue antioxidant effectiveness against lipid peroxidation may be of practical importance in the quantitative assessment of antioxidant interactions.

Gallstones and Obesity

The Nurses' Health Study cohort, started in 1976, has provided important data on gallstones and weight. In 1980 an expanded food-frequency section, including alcohol consumption, was added to the biannual questionnaire. Of the 98,462 nurses who

responded, 88,837 were used in the study on symptomatic gallstones; the remainder were excluded prior to the analyses for incomplete or inconsistent responses or because they had cholecystectomies or symptomatic gallstones prior to returning the questionnaire. The incidence of cholecystectomies and development of symptomatic gallstones was evaluated from 1980 to 1984 in a cohort of women 34 to 59 years of age in 1980.

In the 4-year period under study, 433 women had cholecystectomies and 179 women developed symptomatic gallstones for an overall incidence of about 17/10,000 per year in these middle-age, health-conscious women. The relative risk of symptomatic gallstones (including cholecystectomies) increased approximately linearly with the Quetelet's index (weight in kilograms divided by the square of the height in meters). Among the women who had been only slightly overweight in 1980, (24 to 24.9 kg/m²), the age-adjusted relative risk was 1.7 as compared with women whose relative weight was less than 20 kg/m². Among obese women with a relative weight of 32 kg/m² or more, the age-adjusted relative risk was 6.0. No association with age was found among heavier women (more than 25 kg/m²). In fact, the highest incidence was among the obese women who were 34 to 39 years of age in 1980. Weight gain between the age of 18 and the study was an important factor; those gaining 5 to 9 kg doubled their risk and those gaining 10 or more kg tripled their risk. However, a weight loss between those periods did not reduce the relative risk. This study showed no correlation of parity and gallstones. Finally, in agreement with the results of several other epidemiologic studies and experiments with prairie dogs, an average alcohol intake of 5 g or more per day was associated with a 40 percent reduction in risk among the nonobese women.

Obesity and Genetics

NIDDK-supported researchers have evaluated the differences in response of individuals participating in a long-term overfeeding program to assess the contributions of genetic

and nongenetic sources of variation in changes in body fat content and regional fat distribution. The participants in the study included 12 pairs of young adult male identical twins. The energy requirements of each individual were assessed. Subsequently, their diets were designed to provide 1,000 calories in excess to their daily energy expenditure for 6 out of every 7 days for 100 days. Body weight increased significantly in all subjects with a mean weight gain of 8.1 kg. However, the range in weight gain was from 4.3 kg to 13.3 kg. Both fat mass and fat free mass increased, but the gain in fat mass was greater than the increase in fat-free mass. The increase in weight and total fat mass resulted in a significant increase in resting heart rate and in diastolic blood pressure. Systolic blood pressure was unaltered.

The amount of subcutaneous fat as estimated by skinfold thicknesses increased on both the trunk and limbs, but slightly more accumulated on the trunk. Both the waist and the hip circumference increased significantly, and the ratio of the waist to the hip circumference also increased. Overfeeding also increased the amount of visceral or deep anatomical fat with a wide range of variation among subject pairs. For all methods of assessing biological and physiological changes within this study, the responses observed within each identical twin pair showed significantly less variance than among pairs of identical twins.

The changes in body weight, body composition, trunk fat, and visceral fat deposition varied among the twin pairs studied. Differences between the high weight gainers and the low weight gainers were approximately three-fold.

Individual differences in weight gain in response to overfeeding have been demonstrated previously; however, this study demonstrates them even more clearly, and because the degree of overfeeding was identical for each man and the duration was long enough to induce changes in body composition as well as regional fat distribution, the genetic influence of a comparable surplus of energy intake over a relatively long period could be assessed. These

results strongly support the view that there are individual differences, at least partly related to genetic characteristics, in the tendency towards the development of obesity and in the distribution of body fat.

In another study assessing the relative importance of genetic factors on the presence of obesity, identical and fraternal twins who were raised either together or apart were compared. There were 93 pairs of identical twins raised apart, 154 pairs of identical twins raised together, 218 pairs of fraternal twins raised apart, and 208 pairs of fraternal twins raised together. The study of identical twins raised apart is generally considered to be an effective design for distinguishing the importance of shared genes from that of shared environments. Results indicated that there is a strong influence of heredity on the body mass index (a measure of overweight). Again, the intrapair agreement among identical twins was more than twice as good as for fraternal twins. More importantly, this latter study found that the environment during childhood did not contribute to the variation in body mass index and concluded that environmental influences on body mass index are not attributable to shared family influences but are unique to the individual person.

Renal Diseases

The incidence rate of treated end-stage renal disease (ESRD) has increased by 75 percent from 1977 to 1987. Currently, the two major treatments for ESRD are hemodialysis and kidney transplantation, which are costly and have a relatively high morbidity and mortality associated with them. However, a number of animal studies have shown that a diet with reduced protein and phosphorus content may slow down or halt progression of chronic kidney disease. Likewise, a number of small studies in humans have shown similar promising results but shortcomings in their design have limited their conclusions about the benefits of a low-protein diet on the course of disease.

The adverse effects of high protein diets on renal function and survival have been noted for more than 60 years in laboratory rats. Revival of interest in the adverse role of proteins on renal function is the result of a series of rigorous studies in rats that led to a concept of hemodynamic glomerulopathy. In brief, when renal mass is reduced, intrarenal vascular resistances decrease and a two- to three-fold increase in single nephron plasma flow and single nephron glomerular filtration rate (GFR) ensue. These adaptive intrarenal hemodynamic changes are immediately beneficial in terms of overall GFR; however, in the long run, they have adverse effects on single nephron function, resulting in progressive proteinuria, mesangial obsolescence of the surviving nephrons with progressive decrease in total GFR and death in uremia. A high protein intake accelerates this process, whereas dietary protein restriction reverses the intrarenal hemodynamic changes, prevents the proteinuria, and limits the glomerular sclerosis, thereby prolonging survival.

These events are not limited to the remnant model of kidney disease. A high protein diet induces disease in the remaining kidney after unilateral nephrectomy. Uninephrectomy also accelerates the nephropathy associated with experimental diabetes, hypertension, systemic serum nephritis, puromycin nucleoside nephrosis, and renal irradiation. Again, reduction of dietary protein limits the progression of disease.

Currently a clinical trial supported in collaboration with the Health Care Financing Administration called the Modification of Diet in Renal Disease (MDRD) Study, is under way to determine whether changes in dietary protein and phosphorus and careful control of blood pressure can slow down or stop loss of kidney function. Located at 15 participating clinical centers throughout the United States, MDRD investigators are recruiting and following men and women ages 18-70 who have mild to moderate loss of kidney function.

Recruitment for the study has been encouraging; 400 of the 800 required study participants have been entered into the study thus far. In addition, significant advances have been made regarding precise measurement of kidney function at multiple study sites as well as development of a state-of-the-art dietary intervention and patient education materials. It is anticipated that results from this investigation will be available in 1993.

RESEARCH DIRECTIONS

The NIDDK fosters and supports other nutrition research and training, especially in the following broad areas of fundamental and clinical nutrition:

- Research on dietary requirements (and safe levels) of many nutrients needed for health maintenance, proper growth and development, and a state of well-being at all ages and under various conditions such as stress, drug use, nutrient imbalances, and changing activity levels.
- Fundamental studies exploring nutritional factors that are active in absorption and metabolism, the biological control of such processes, and the identification of unrecognized roles of nutrients or their metabolites.
- Studies on the detrimental effects of iron deficiency in terms of such factors as work capacity and performance, physical and mental development and function, susceptibility to infection, and perinatal morbidity and mortality.
- Assessment of the impact of omega-3 fatty acids on prostaglandin biosynthesis and metabolism, their influence on membrane function, and their potential role in the development and progression of disease processes.
- Research on fiber to determine its chemical characteristics in order to determine its effects on intestinal microflora and food transit time; its interaction with nutrients, bile acids, and other substances in the gut; its effects on digestive enzymes and absorption; and the development of improved routine methods for analyzing its components.
- Assessment of the requirement levels and metabolic roles of trace elements, with the help of reliable, newly developed, analytical methods.
- Research on relationships between genetic predisposition, induced metabolic changes, thermogenesis, environmental and physiological factors, and lifestyles that result in greater energy intake than expenditure (for obesity prevention and control).
- Development of methods for characterization of various types of obesity and determination of the health consequences of repeated cycles of weight gain and loss.
- Investigation of how chronic feeding of diets high in fat and glucose increases blood pressure and enhances sympathetic nervous system activity in rats.
- Studies of the mechanism and efficacy of pharmacologic agents on energy balance and weight control.
- Research on the diverse alterations in carbohydrate metabolism seen during injury or infection in rats.
- Investigations on how dietary polyunsaturated fats uniquely regulate fatty acid synthesis.
- Determination of the most effective individual, group, and community intervention strategies for weight management.
- Investigation into the contribution of genetic and metabolic factors to obesity causation, including the molecular and genetic basis of energy metabolism and the nature of genetic aberrations in human obesity.
- Research to improve nutritional support to hospitalized patients, to improve nutritional status assessment methodology, and to acquire more information about the effects of disease states on the nutritional needs of patients.
- Investigation of dietary modifications that may retard the rate of progression of endstage renal disease, reduce the need for dialysis, or both.
- Research to determine the relationship of

the role of dietary protein to that of phosphate in protein's effect on kidney function.

- Investigation of the mechanisms by which other nutrients such as fatty acids or amino acids might affect renal function.
- Studies of the causes of wasting malnutrition and other nutritional disorders that occur in renal failure.
- Research on the interplay of dietary factors (such as calcium, vitamin D, phosphate, protein, and oxalate) in the etiology of renal stones.
- Studies on hormones that regulate bone metabolism, nutrition and nutrient metabolism and the maintenance of calcium balance, especially as related to osteoporosis and related bone disorders.
- Studies to elucidate the endocrine and metabolic basis of wasting in AIDS.
- Research on the role of cachectin and/or other monokines in the pathogenesis of wasting in AIDS and other chronic diseases.
- Studies on the role of calorie intake and physical activity, and subsequent weight control, in the prevention of Type II diabetes.
- Investigation of the metabolic mechanisms of intestinal and hepatic processing of dietary carbohydrate, and the effects of other nutrients and of fiber on carbohydrate metabolism.
- Clinical research into nutrition-related areas such as cholesterol and pigment gallstones; inborn errors in bile acid metabolism; chronic hepatitis that evolves from autoimmune, viral, or alcoholic disease; and various liver diseases such as Wilson's disease and portal hypertension.
- Investigations into the control of appetite, satiety, and anorexia in normal individuals as well as in those with various disease states.
- Exploration of mechanisms for the development of gastrointestinal malabsorption in AIDS patients and investigations of other metabolic perturbations of nutrient metabolism such as lipogenesis to develop rational means of nutritional support of these patients.

- Funding of five Clinical Nutrition Research Units and the Obesity Core Center, each conducting an intensive program of nutrition research.
- Identification of hormones, growth factors, lipid mobilizing factors or other peptides which may contribute to wasting in AIDS.
- Regulation of muscle mass and nitrogen balance in AIDS.
- Studies of whether abnormalities in insulin secretion or sensitivity may be involved in decreased fat stores in AIDS.

OUTLOOK

The NIDDK's investigations into nutritional requirements in health and disease and into the role of diet in disease prevention and health promotion ultimately will affect national health and productivity.

The NIDDK has specifically recognized the importance of obesity as a public health problem. There is a great need for basic understanding of the mechanisms of energy balance and other physiologic parameters that lead to the development of obesity. New initiatives are being targeted to address this important problem.

Working in conjunction with other NIH institutes, the NIDDK shares responsibility for advancing fundamental knowledge of the processes and programmatic changes that will lead to needed alterations in American dietary habits.

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NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

Created in 1950, the NINDS supports and conducts research and research training on the brain and the nervous system, and neurological and neuromuscular disorders. These disorders include brain and spinal cord trauma, Parkinson's disease, Huntington's disease, epilepsy, stroke, aphasia, brain tumors, neuro-AIDS, multiple sclerosis, muscular dystrophy, Batten's disease, Gaucher's disease, amyotrophic lateral sclerosis, and sleep disorders. This mission is accomplished through the NINDS Division of Fundamental Neurosciences; Division of Convulsive, Developmental, and Neuromuscular Disorders; Division of Demyelinating, Atrophic, and Dementing Disorders; Division of Stroke and Trauma; and Division of Intramural Research.

On July 25, 1989, President Bush signed into law a House Joint Resolution which declared the 1990's the "Decade of the Brain," calling upon the Nation to observe the decade with appropriate activities. Recent years have witnessed tremendous progress and exciting achievements in brain and nervous system research. Upon this base, the NINDS has identified numerous compelling neurological disease areas and research issues for which opportunities exist to make extraordinary advances within the decade of the nineties.

As more is learned about the brain, the extent of the interaction between nutrition and the nervous system is evolving and rapidly changing; however, many issues are still controversial and inconclusive. The NINDS nutrition research program continues to support studies to clarify the relationship between nutrient intake on the central nervous system and conversely, the influence of the brain in the etiology of obesity as well as dietary patterns that may prevent and treat various neurological disorders.

PROGRAM HIGHLIGHTS

Role of Diet in Stroke and Cerebrovascular Disease

Stroke ranks as the third leading cause of death in the United States, occurring in about 450,000 persons per year. Many who survive are left with enduring crippling disabilities. Additionally, stroke is a major and increasing cause of the late-life dementia that affects more than two-fifths of Americans who live beyond their 80th year. Stroke is the most common cause of disability requiring rehabilitation, imposing enormous social and financial costs amounting to well over \$25 billion annually.

The effects of eating patterns on the causation of stroke are under investigation. Several longitudinal population studies have collected data on a variety of determinants, including diet, that may be risk factors for stroke. Epidemiologic evidence associates excessive alcohol consumption with increased frequency of subarachnoid hemorrhage and cerebral infarction; therefore, heavy alcohol intake may be an independent risk factor for stroke.

Hypertension is a major risk factor for stroke. Evidence links dietary factors to high blood pressure and also supports the relationship between dietary fat, blood cholesterol and atherosclerosis, especially of the *coronary* arteries. However, a similar association with intracranial *cerebral* arteries and stroke is not as firmly established.

Neural Tube Defects

Spina bifida is classified as a birth defect among what are collectively known as neural tube defects (NTDs). Spina bifida is one of the

most prevalent birth defects and is the leading disabler of newborns in America. It occurs in 1 to 2 out of every 1,000 babies born in the United States. The disorder begins in the first month of gestation, when for reasons still largely unknown, the spine fails to form properly. Studies are focusing on congenital, environmental, and nutritional factors.

Data from recent studies suggest that vitamin deficiencies are important contributors to NTDs. This theory results from two types of studies—those which show low vitamin and folic acid blood levels in pregnancies with NTDs, and those in which a marked decrease in the incidence of NTDs was found when vitamin supplements were used. Recently, British scientists studied how prenatal vitamins affected the occurrence of spina bifida in babies born to women who previously had delivered a child with the disorder. They found that women who took a vitamin supplement with folic acid before conception and during part of pregnancy subsequently had one-seventh the number of babies with spina bifida compared to a similar group of women who did not take vitamins. A related study in Newfoundland, which has the highest incidence of NTDs in North America, confirms the earlier British findings suggesting that dietary factors may be of etiologic importance in the occurrence of NTDs. However, it also may be that children with NTDs have a defect in the way their bodies process the folic acid they receive. Other investigators speculate that several vitamin shortages could work together to interfere with neural tube development. Continued research will help determine the precise role of vitamins and other factors in the development of spina bifida.

In a major 5-year epidemiologic research project supported by the NINDS at Boston University's Center for Human Genetics, scientists have been studying 25,700 pregnancies, focusing on neural tube defects and specifically seeking associations between such defects and periconceptional vitamin A and folic acid consumption, hyperthermia, and other environmental and genetic factors. This

study is an important addition to previous studies because it is a prospective study of a large group of women at high risk, studied in a single center, and includes follow-up of the children born during the study to 1 year of age.

Neurotoxins

NINDS scientists have reported that a novel toxin, N-butylbenzenesulfonamide, a plasticizing agent used commercially in the manufacture of plastic containers, caused a spastic myelopathy in experimental animals. Some types of plastic food containers have been shown to leach polymerizing compounds into the food contents. These findings will be pursued to answer important questions about the role of such agents in neurodegenerative disorders of unknown etiology.

Aluminum is one of several metals suspected of having potent toxic effects on the central nervous system. In recent decades evidence has accumulated that aluminum may play a key role in dialysis encephalopathy, amyotrophic lateral sclerosis and parkinsonian-dementia of Guam, and in Alzheimer's disease. Infants, particularly those born prematurely, are also especially susceptible to aluminum overloading and toxic side effects, including damage to the central nervous system.

Other Research

NINDS is supporting the study of aspartame, a commonly used artificial sweetener, which may present potential hazards to the developing fetus. Because phenylalanine has been shown to be responsible for most of the toxic effects of aspartame, this substance will be administered to pregnant animals, and offspring will be neurologically evaluated.

RESEARCH DIRECTIONS

The following are among the many relevant issues which, through investigation, may help clarify the relationship of diet and neurologic function:

- The nutritional needs of the brain and nervous system to maintain its health throughout life.
- Understanding the blood-brain barrier nutrient transport process.
- The relationship, if any, between specific dietary factors and certain brain functions such as memory, alertness, and response time.
- The effects of excessive intake of nutrients and supplements on nervous system function.
- The role of specific dietary factors in the etiology and prevention of neurologic disorders such as stroke, Alzheimer's disease, and Parkinson's disease.
- The identification and role of dietary-derived neurotoxins.

OUTLOOK

Rapid research advances in the neurological sciences have been realized, creating opportunities to prevent, cure, or alleviate the many neurological disorders now afflicting many Americans. Studies elucidating the role of nutrients, food additives, and general dietary patterns in the development and subsequent function of the brain and nervous system will continue to be supported by NINDS during the 1990's—the Decade of the Brain.

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NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Although the NIAID was established in 1948, it traces its roots back to the Laboratory of Hygiene, a bacteriological laboratory which was founded in 1887 and was the forerunner of the NIH and the NIAID. The NIAID supports basic and clinical research in microbiology, infectious diseases, immunology, and allergy. A major component of NIAID's basic research is concerned with fundamental life processes as exemplified in microorganisms and in animal cells *in vitro*. Techniques and basic biologic principles, developed as a result of this fundamental research in microbiology and immunology, have then been applied to the other areas of biology and medicine, including nutrition.

The complex interrelationships among nutrition, microbial infections, and immunology have important health implications. In the developing world, more than 1 billion cases of infectious diarrheal disease occur yearly in children under the age of 5 years. Malnutrition both predisposes to diarrhea and occurs as a result of diarrhea. Immunodeficiency states, such as AIDS, cause malnutrition and set the stage for superinfections which accelerate the cycle of malnutrition and infection. Asthma and allergic diseases affect over 40 million Americans. Surgery and trauma lay the groundwork for infection and subsequent malnutrition. Many of these infections or their complications can be mitigated, at least in part, by appropriate nutrition.

PROGRAM HIGHLIGHTS

NIAID's studies on nutrition are an integral part of the Institute's research to lessen the adverse health consequences of immunologic and infectious diseases. Of particular significance are the consequences of wasting on the underlying AIDS disease process, its infectious and immunological complications, and the outcome of antimicrobial drug therapy.

Continuing concerns are the prevalence of infections among the malnourished, the effect

of infections on nutritional status, the prevalence of food-borne microbial illness and its control, and the effect of malnutrition on resistance to infection, especially to infectious diarrhea in young children.

Additional interests include the following:

- The infectious and immunological complications of surgery and trauma, the dissection of the underlying immunological mechanisms involved, and better control through immunological and nutritional means.
- The effects of iron, zinc and related elements on microbial virulence.
- Investigations concerning whether food allergy plays an important role in gastrointestinal disease.

AIDS and Nutrition

Since the recognition of AIDS in 1981, the NIAID has mounted a coordinated and comprehensive program of basic and clinical research against AIDS and its microbial and immunological complications.

Infection by the immunologically devastating human immunodeficiency virus (HIV-1) sets the stage for weight loss and deteriorating nutritional status. Common features of advanced AIDS are anorexia, vomiting, diarrhea, malabsorption of fats, carbohydrates, protein and other nutrients, and a profound cachexia. One goal of NIAID's mission of developing and testing potentially useful drugs against AIDS is the maintenance of AIDS patients in optimal health. Weight loss, whose onset often precedes the diagnosis of AIDS, can be so severe that it interferes with anti-viral drug therapy and predisposes to superinfections by other microbial agents.

Recent studies have indicated, for example, that malnutrition in Americans with AIDS is so pronounced that body cell mass near the time of death averages just slightly over 50 percent of normal and that total body weight is 33 percent

below ideal body weight. This degree of wasting is similar to that reported for fatal starvation, as in the siege of Leningrad during World War II. These observations would suggest that better supportive nutritional therapy could significantly prolong survival in AIDS patients.

In a study from the NIAID's Intramural Program, low serum vitamin B₁₂ levels were found in some patients with AIDS but a majority of AIDS patients had abnormally low absorption of B₁₂-intrinsic factor complex. Each of these latter patients had mild to moderate chronic inflammatory changes in duodenal and colonic biopsy specimens. In a subsequent study of patients who were HIV-1 positive but without AIDS, 7 percent were found with low serum B₁₂ levels. Since several years are required to produce B₁₂ deficiency, these low serum B₁₂ levels reflect a long-standing abnormality of intestinal function associated with HIV-1 infection. The significance of B₁₂ deficiency on clinical outcome in HIV-1 infection and its possible deleterious effect on drug therapy remain to be determined.

Immunology and Nutrition

Severe malnutrition due to any cause will impair the body's normal cell-mediated immunity and may diminish the immunity effected by antibodies.

Lack of appropriate amounts of trace elements in the diet may contribute to severe immunologic deficits. Deficits of trace metals such as iron and zinc are already known to impair neutrophil function. Of particular significance are the effects of specific unsaturated fatty acids on immune functions in infections, allergies, immunologically mediated diseases, and transplantation.

Food Allergy

Food allergy may play an important role in gastrointestinal disease, but little is known

concerning how widespread the problem is, its mechanism of action, and its control. An NIAID-sponsored Food Allergy Working Group has been established to develop clinical criteria, to furnish standardized food allergy preparations, to develop appropriate *in vitro* assay materials and methodologies, and to conduct clinical studies of food allergens using standardized protocols. Investigators also are developing standard diagnostic tests to determine who may be at risk from allergic reactions to foods.

Other NIAID-supported research has studied the natural history, immunopathophysiology and potential diagnostic, and therapeutic aspects of IgE-mediated food hypersensitivity in children with atopic dermatitis. During the past 7 years, a NIAID-supported grantee has studied children with severe atopic dermatitis for food hypersensitivity. A large percentage of patients reacted to one or more foods. Abstinence from the offending food led to significant improvement in eczematous signs and symptoms and loss of symptomatic sensitivity in one-third of children studied.

Increasing recognition of the role of food allergies in disease should lead to better diagnosis, improved patient care, and eventually to the prevention of these food-induced diseases.

RESEARCH DIRECTIONS

NIAID's interest in nutrition aims at a better understanding of the complex inter-relationships of nutrition, immunity, and infection. The Institute's research directions are correspondingly varied. They include the following:

- AIDS and nutrition.
- The negative effect of malnutrition on resistance to tropical infections (especially infectious diarrheas) and the role of breast milk as a defense against enteric infections.
- The significant morbidity and mortality of rotavirus-induced infectious diarrhea among infants in developing countries and a major

- effort to develop a safe, effective, and practical rotavirus vaccine for newborns.
- The role of minerals, especially iron, on the metabolism and virulence of bacteria and fungi.
 - The role of nutritional factors in the immune response to animal parasites that cause significant human disease, e.g., schistosomiasis, giardiasis, and cryptosporidiosis.
 - Infections in American hospitals, including the effect of surgery on immune function, hypercatabolism, and resistance to infection.
 - The modulating effects of specific nutrients (e.g., vitamins, trace elements, fatty acids, fiber, and amino acids) on basic immune function.
 - The relationship of specific foods to allergic reactions such as anaphylaxis and eczema, the immune response to ingested antigens including milk, soy and egg, and the role of foods in immunologically mediated gastrointestinal diseases such as sprue and inflammatory bowel disease.

OUTLOOK

Although significant advances have been made during the past decade in acquiring new knowledge of the interactions among nutrition, infections, and immune disorders, much remains to be learned of this complex interrelationship. Intensified research on infectious diseases such as AIDS may provide scientific advances that help to clarify these important, unresolved questions.

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NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

The principal mission of the NIGMS is to support fundamental research that undergirds all biomedical investigations. The major focus of the institute is on research concerned with expanding knowledge of fundamental biological structure and function at the cellular and molecular level. Extramural studies supported by the Institute include investigations in the biophysical sciences, the physiological sciences, in particular, the response of the whole body to trauma, the structure and function of the cell, the basic mechanisms of heredity, and the molecular aspects of the interactions between therapeutic drugs and agents and their target cells, tissues, or organs.

PROGRAM HIGHLIGHTS

The great majority of the nutrition-related research supported by NIGMS is in its trauma and burn injury program area, which focuses on the mechanisms involved in the body's systemic responses to trauma. Thus, research on the role of nutrition in decreasing morbidity rates for patients who suffer serious trauma or burn injury is of significant interest to the Institute. NIGMS-supported scientists are exploring nutritional requirements following severe trauma and sepsis, new concepts in parenteral therapy, branched chain amino acid feeding during injury, and cellular function during septic and hemorrhagic shock. In addition, there are studies being supported which are investigating the cellular changes and mechanisms responsible for the protein wasting associated with nutritional deprivation.

Nutrition and Trauma

It has been established that changes in metabolic patterns and nutritional status play an important role in the development of sepsis and multiple organ failure as well as in the recovery from severe injury, including surgical trauma. Recent highlights in the area of nutritional requirements and therapy in the traumatized patient have focused on the effects

of diet in the development of septicemia following surgical and burn injury.

Specifically, bacterial infection is a frequent and serious problem in patients who survive the initial shock phase of thermal injury. Infections in burn patients generally have been considered to arise from exogenous organisms colonizing the burn wound. Until recently, very little attention has been directed to the indigenous microflora in the gastrointestinal tract of the burn patient as a source of the repeated episodes of bacteremia; yet, the gut may serve as a reservoir for organisms causing bacteremia in the burn patient. Bacterial translocation has been defined as the passage of viable bacteria from the intact gastrointestinal tract to the mesenteric lymph nodes and eventually into the systemic circulation. It has been speculated that the GI tract may cause the infections, either indirectly by fecal organisms contaminating and colonizing the wound, or directly by passage through the intestinal wall. NIGMS-supported researchers have shown that feeding animals an elemental diet promotes spontaneous bacterial translocation and increases mortality in these animals after an injection of *E. coli* endotoxin. Endotoxin challenge also was associated with higher levels of serum tumor necrosis factor (TNF), an endotoxin-induced macrophage product which produces cachexia. While the mechanisms responsible for these changes are not known, these investigators have speculated that bacterial translocation related mortality may in part be an amplified cytokine response to endotoxin.

Grantees supported by the NIGMS also have demonstrated that chronic administration of TNF in experimental animal models reproduces many of the physiologic findings observed in the chronic wasting of clinical disease. During repeated doses of TNF, there is a consistent decrease in food intake in rats and mice, decreased nitrogen balance, and weight loss. Concomitant administration of antibody to TNF is successful in blocking these effects. Chronic

starvation elicits a preferential mobilization of fat stores with a relative sparing of skeletal muscle. Also, in acute starvation there is a marked wasting of liver protein accompanying the loss in peripheral mass. By contrast, chronic TNF administration produces an exaggerated peripheral skeletal muscle wasting with a preservation of liver mass similar to that observed in injured patients.

NIGMS-supported researchers were among the first to demonstrate that TNF markedly suppresses the activity of lipoprotein lipase, the enzyme which catalyzes the hydrolysis of lipoprotein derived triacylglycerol, providing fatty acids for storage or catabolism.

Total parental nutrition (TPN) has favorably influenced the clinical outcome of many malnourished and injured patients unable to receive nutrients by the enteral route. Recent evidence by researchers supported by NIGMS suggests that significant differences in response to infectious insult may exist between the enterally and parenterally fed states. These investigators have produced data which suggest that bowel rest produces alterations in host resistance to injury, independent of malnutrition. Other investigations are providing evidence that intravenous refeeding blocks growth hormone provoked rises in serum free fatty acids. In addition, hyper-alimentation induces a metabolic background which inhibits growth hormone secretion.

RESEARCH DIRECTIONS

The following leads are being pursued which pertain to basic research on diseases and also traumatic injury:

- The role of diet in organ and cellular responses to cytokines.
- Change of metabolic patterns and nutritional requirements following severe injury.
- Hormonal imbalance following injury and its effects on metabolism.
- Mechanisms involved in producing a protein catabolic state after injury.

- Adaptive regulation of nutrient transport by the gut. Transport appears to be governed by nutrient-receptor proteins on specific cell surfaces.
- Mechanism of suppression of lipoprotein lipase activity by TNF. Pools of mRNA which code for the lipase are perhaps depleted in the presence of TNF.
- Which components of the host defense system (neutrophils, immunomodulators, etc.) are important in preventing bacterial translocation.
- Receptors that recognize serum proteins carrying galactosyl sugar residues, including hormones that regulate the rate and extent of nutrient uptake and processing in the liver.

OUTLOOK

Research supported by the NIGMS serves to establish the foundation of new knowledge needed to make advances in the understanding of many diseases. Those investigations which are nutrition-related will help to provide the concepts and relevant information necessary to develop new treatments and hence, serve to decrease morbidity and mortality.

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NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Since the NICHD was created in 1963, its nutrition research program has focused on the continuum of human development, from conception through infancy, childhood, and adolescence. The program emphasizes preventive approaches to nutrition-related conditions and stresses health promotion as well as disease prevention. Much of the research is multidisciplinary in nature and involves the genetic, biochemical, developmental, anthropometric, behavioral, and cultural aspects of nutrition. The NICHD supports research on maternal and fetal nutrition; nutrition during infancy, childhood, and adolescence; the relationship of nutrition to reproduction; behavioral and cultural aspects of nutrition; obesity and its nutritional antecedents; nutritional therapy of inborn errors of metabolism; and assessment of nutritional status.

PROGRAM HIGHLIGHTS

The Institute has a strong interest in the nutrient requirements of normal, premature, and low birth weight infants, as well as in the composition of human milk, cow milk, and synthetic formulas, in relation to optimal infant nutrition. In some of this work the interest centers on metabolic processes in neonatal adaptation and on the role played by essential nutrients and other components of human milk. Research on cultural and behavioral determinants of nutritional individuality includes studies of habits, taste, and olfaction; food avoidances; and behavior modification of dietary intakes. Research on nutritional antecedents of adult disease focuses primarily on factors in the development of obesity in infancy, childhood, and adolescence.

Adrenoleukodystrophy

Adrenoleukodystrophy (ALD) is an X-linked disorder characterized by the accumulation of saturated very long chain fatty acids (VLCFA) due to a genetic defect of a peroxisomal enzyme that normally degrades these substances. ALD affects mainly the nervous system white

matter, adrenal cortex, and testis. Recent studies have demonstrated that adherence to a diet low in fatty acids combined with daily doses of glyceroltrierucate (the chemical name for rapeseed oil derivative) can bring those fatty acid levels under control. A study has recently been initiated to test whether early normalization of saturated VLCFA can prevent or ameliorate the neurological impairment associated with ALD. The study has three components: 1) a double-blinded trial involving adults with adrenomyeloneuropathy and neurologically involved ALD heterozygotes; 2) a prevention trial for neurologically asymptomatic boys with ALD; and 3) a study of neurologically symptomatic boys in whom the rate of neurological progression will be compared with that in more than 100 untreated children with ALD.

Maternal Phenylketonuria

The success of newborn screening programs for phenylketonuria (PKU) has created an unexpected problem as women with PKU reach childbearing age. Retrospective surveys have shown a high rate of mental retardation, microcephaly, congenital heart defects, and intrauterine growth retardation among offspring of women with PKU who were not maintained on a diet with restricted amounts of phenylalanine during pregnancy. An ongoing collaborative study suggests that, to achieve an optimal reproductive outcome, the diet should be initiated prior to the 10th week of pregnancy, and preferably before conception. The diet should be maintained throughout pregnancy, and the blood phenylalanine level should be kept at 6 mg/dL or less.

Omega-3 Fatty Acids in Premature Infants

It has been known for some time that certain fatty acids are essential in the human diet. In general this requirement has been considered to be met by the provision of fatty acids of the omega-6 class. A possible need for omega-3 fatty acids as well has been suggested by

observations of patients receiving parenteral nutrition and by studies in newborn monkeys. The issue is important because most milk formulas for prematures, in contrast to human milk, are very low in omega-3 fatty acids. Now NICHD-supported research has demonstrated that there is a delay in maturation of the rod cells, light receptors of the retina, in very low birth weight babies receiving formulas low in long chain omega-3 fatty acids. Though rod function returned to normal by the time the infants reached 57 weeks post-conceptual age, the results suggest that the omega-3 content of these premature formulas is insufficient for optimal visual development of very low birth weight infants. The mechanism of this developmental delay in vision needs to be determined, along with its significance to the long-term visual and behavioral function of these babies.

Calcium Transport to the Developing Chick Embryo

Calcium is a major nutritional requirement for vertebrate embryonic development, required for physiological functions such as skeleton formation, neuromuscular activity, and blood coagulation. In avian species the chorioallantoic membrane transports calcium from the eggshell to the developing embryo, and it can be used as a simple experimental model for the study of transplacental calcium transport.

Several components of the chick calcium transport system have been identified by an NICHD-supported investigator. A specific calcium-binding protein, localized on the surface of calcium-transporting ectodermal cells of the chorioallantoic membrane, functions as a calcium receptor. It is activated during development by an enzymatic reaction which is dependent on vitamin K. The calcium is incorporated into a vesicle inside the cell, from which it is eventually released by a mechanism which involves acidification of the vesicle. Near the receptor on the cell surface is a calcium-activated ATPase which somehow functions intracellularly to maintain the

vesicular calcium load. These studies contribute to a specific understanding of calcium transport as well as to a general understanding of developmental functions and their nutritional regulation.

Low Birth Weight Initiative: Necrotizing Enterocolitis

In the United States, the most important factor contributing to the infant mortality rate is a birth weight of less than 2,500 g, or 5.5 lbs. At present, 6.7 percent of all U.S. babies weigh less than 2,500 g at birth and are termed low birth weight infants. In FY 1985, the NICHD inaugurated the Low Birth Weight Initiative in order to focus more research attention on the nationwide problem of infant mortality and birth weight specific mortality. The nutrition component of this initiative is divided into several critically important facets: nutritional management in pregnancy, nutritional management of the very low birth weight (VLBW) infant, and gastrointestinal development.

As part of this initiative, NICHD has developed a multicenter research network to evaluate the causes and treatment of major clinical problems affecting neonatal survival. Seven centers participate in this collaborative project, called the Neonatal Intensive Care Unit (NICU) Network, prospectively collecting data on approximately 2,000 very low birth weight (<1,500 g) neonates per year. Standardized data collection systems and common definitions to describe perinatal variables are used.

Because necrotizing enterocolitis (NEC) has emerged as a significant cause of morbidity and mortality in very low birth weight neonates, the NICU Network conducted a retrospective evaluation of 3,317 of these infants in participating centers. The overall incidence of proven NEC was 8.7 percent, with a highly variable prevalence among centers (range 19.5 percent to 3.4 percent). The study examined the effect of demographic variables, perinatal events, other early morbidity, and fluid and

nutritional management on NEC. Analysis of this sample suggested the importance of fluid and nutritional practices on the prevalence of NEC in VLBW infants. More aggressive feedings and more rapid regain of birth weight were associated with a higher prevalence. Black male infants were at most risk, and the age of onset of NEC was inversely related to birth weight and gestational age. A large case-controlled study (matched for those factors noted to be significantly related to NEC) of the effects of parenteral fluids and volume expanders and enteral drugs and feedings on the incidence of NEC is planned for FY 1991.

RESEARCH DIRECTIONS

The NICHD is nearing completion of work with a group of consultants on the development of a new Institute Five Year Plan for Nutrition Research and Training. The aims of the plan are as follows:

- To identify the global issues in maternal-fetal, neonatal, infantile, childhood, and adolescent nutrition.
- To pose key questions about these global issues, including epidemiologic questions.
- To identify the technology needed to address these key questions.

The plan is expected to have an important influence on the activities supported by the NICHD, providing information needed for the development of areas of emphasis and the allocation of resources for nutrition research within the Institute's programs. Subjects identified for attention thus far in the new Nutrition Research Plan are nutritional epidemiology and international nutrition, trace elements and micronutrients, nutritional therapy of inborn errors of metabolism, obesity and energy metabolism, feeding of low birth weight and term infants by enteral and parenteral nutrition, lipoproteins and antecedents of adult vascular disease, nutritional influences on gastrointestinal development, maternal-fetal nutrition, fetal growth factors, nutrition and brain development, and human milk research. It is

expected that the new plan will be completed in FY 1990.

A few examples of current nutrition research supported by the NICHD are as follows:

- Studies on the effects of vitamins on reproductive function and morphology, and on the relationship between oral contraceptive use, cervical dysplasia, and folate levels.
- Maternal-fetal nutrition research on the mechanisms of placental transfer of essential nutrients and the influence of these nutrients on normal and abnormal fetal development.
- Studies of events governing development of the gastrointestinal tract from fetal life to adulthood. The role of human colostrum and milk in stimulating development of the gastrointestinal tract and protecting it from disease are of special interest.
- Studies of human milk, cow milk, and synthetic formula to assess the requirements for optimal growth and development in normal and LBW infants.
- Research on the nutritional antecedents of various adult diseases, including the nutritional ramifications of diabetes in pregnancy for infants born to diabetic mothers; the development of obesity in infancy, childhood, adolescence, and early adulthood; and dietary, genetic, and metabolic precursors of atherosclerosis.
- Studies of behavioral, neurochemical, genetic, and hormonal factors in childhood obesity.
- Studies of the influence of nutritional factors on cognitive development and behavior in both normal subjects and patients with inborn errors of metabolism.

OUTLOOK

NICHD's nutrition research focuses on human development beginning with conception and continuing through infancy, childhood, and adolescence. The program emphasizes research on preventive approaches and stresses health promotion as well as treatment.

As progress is made in NICHD-supported laboratories and clinics, the findings become available to improve the outlook for babies born in this country and throughout the world.

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Since its establishment over 20 years ago, the NEI has dedicated itself to reducing the prevalence of blindness, visual impairment, and eye disease in the United States and throughout the world. For the past year, the Office of International Program Activities has been the focus of these activities, including activities to understand, alleviate, and prevent nutrition-related blindness.

As much as 80 percent of the forty million cases of blindness worldwide are considered curable or preventable. Xerophthalmia, a potentially blinding disease caused by vitamin A deficiency, is the leading cause of nutrition-related blindness and visual impairment among the world's children. It accounts for 70 percent of the estimated 1.5 million blind children in the world. Mild vitamin A deficiency with consequences for child health and survival affects another 20 to 40 million children worldwide.

PROGRAM HIGHLIGHTS

The NEI supports research on the role of general nutrition and on specific nutrients such as vitamins A, C, B₆, and E, as well as protein, copper, and zinc on normal ocular and visual development, health, and function. Scientists supported by the NEI also are examining the association between nutritional imbalances and eye and vision disorders, such as cataract, retrolental fibroplasia, retinitis pigmentosa, gyrate atrophy, macular degeneration, and other visual disabilities.

Vitamin A and the Ability to See and Survive

Xerophthalmia is directly linked to dietary deficiency of vitamin A. Worldwide, it is estimated that 700,000 annually develop corneal disease of which 60 percent die and of those remaining at least 250,000 are partially or totally blinded annually by this preventable cause. An additional 5 to 10 times as many children have their vision mildly impaired by vitamin A deficiency, and an equally large

additional group of children are subclinically deficient and may have their general health status compromised, thus contributing to high childhood mortality rates.

Vitamin A, or retinol, plays an important role in the visual process, particularly through the generation of visual pigments. NEI-supported investigators are studying the basic metabolism of vitamin A in ocular tissues and the interactions of this vitamin with other nutrients such as vitamin E, vitamin C, and zinc. Scientists also are examining the synthesis, metabolism, and molecular structure of retinol-binding proteins and their functions in the eye because deficiencies of these proteins or alterations in their binding properties appear to compromise the normal function of vitamin A in the retina and in the pigment epithelium of dystrophic eyes.

Field-based studies with collaborators in India have demonstrated the effectiveness in reducing mortality by raising the level of vitamin A intake of preschool-age children to the recommended level through a weekly supplement delivered by community workers. The effect of this moderate improvement in vitamin A nutriture on the incidence of ocular, gastrointestinal, and respiratory morbidities is currently being evaluated.

Age-Related Cataract

Cataract is the leading worldwide cause of blindness and visual disability, affecting about 17 million persons in both industrialized and developing countries. By far the most common of the many different kinds of cataract is age-related cataract, the result of which persons prematurely lose their productive potential. Although surgery is an effective cure, currently there is no known way of preventing or delaying the onset of such cataracts.

NEI-sponsored case control studies with similar research designs in the United States, Italy, and India have investigated possible personal and environmental risk factors for cataract, including diet, disease history, and

environmental exposures. These studies have been completed, and the data from India suggest that, among several other risk factors, diets low in selected nutrients and a decreased body mass index can be associated with increased risk of some types of cataract. Apparently better nourished persons in India have less risk of cataract. Cross-country consistency in nutritional and other risk factors is now being sought.

Age-Related Macular Degeneration

Although age-related macular degeneration (AMD) is the leading cause of newly registered blindness in the white population over age 65 in the United States, its cause is still unknown. NEI intramural scientists are treating patients who have severe visual loss because of AMD in one eye yet who have good vision in the second eye. This investigation will determine whether the good eye can be protected from severe visual loss by the administration of vitamin E and vitamin C and by diminishing exposure of the patient's retinas to light below 500 nm. Patients recruited for this study are being randomly assigned to either a treated or untreated control group and examined at 4-month intervals. This study will obtain data that are expected to enhance the understanding of AMD while investigating a method for its treatment.

Vitamin A and Ocular Tissues

NEI intramural scientists are studying the role of specific retinoid-binding proteins such as interphotoreceptor retinoid-binding protein (IRBP) in mediating the action of retinoids in both normal and diseased ocular tissues. IRBP, which is thought to be a transport protein for retinoids during the visual cycle, also may be involved in the transport of fatty acids that are essential to normal photoreceptor cell function.

RESEARCH DIRECTIONS

The following projects represent many of the nutrition-related research areas supported by the NEI:

- Investigations into vitamin A, its derivatives, and the proteins that bind it to cells and transport it between and within cells is a major focus of NEI-supported investigations. Scientists are exploring the role these substances play in the normal metabolism of ocular tissues and in the visual process. Alterations of ocular tissue integrity and of its metabolism brought about by chronic deficiency of vitamin A also are being studied. These investigations include studying the role of vitamin A in maintaining the immune competence of the eye and the ability of ocular tissues to respond to infections and trauma.
- Operations research studies related to prevention of vitamin A malnutrition, which is the major cause of preventable blindness among children in the developing world, are under way. Scientists are conducting epidemiological studies to identify the nutritional and environmental factors that act with vitamin A deficiency to increase the risk of developing xerophthalmia and the irreversible corneal damage and destruction caused by keratomalacia. Methods for assessing the relative vitamin A status of individuals also are being evaluated.
- NEI-supported scientists are using dietary assessment interviews to determine the intake of 17 major nutrients and alcohol in a community of 4,800 older adults. Blood samples are being analyzed to measure levels of potentially important nutrients for which dietary estimates are difficult to obtain or for which there are inadequate measures to evaluate their nutrient status.
- Investigators are studying the cloning and sequence analysis of the human gene responsible for encoding the cellular retinaldehyde-binding protein from retina. Because of the possible involvement of this gene in hereditary retinal diseases such as retinitis pigmentosa, scientists are attempting to confirm the cellular localization of this protein by *in situ* techniques and to determine the chromosomal location of the human gene. Scientists believe that the combined results from this research will provide a precise

molecular framework in which questions concerning the normal function of this protein and the visual disorders it may be associated with can be answered in specific terms.

- Scientists are studying the mucosal immunity of the eye, particularly the response and function of the rat ocular secretory immune system, with emphasis on the impact of aging and nutrition on immunological activity in the eye. These investigations address the functional role of the secretory immune system, which serves as the first line of defense to protect the ocular surface against bacterial colonization and viral invasion.
- Scientists are studying the roles of vitamins E and C in nourishing ocular tissues and in maintaining visual acuity during natural and induced chronic and acute exposure to oxidants.
- The NEI also supports research on cataract and macular degeneration, both of which are major causes of visual disability and blindness. The nutrient environment in which cataract and macular degeneration develop and the potential for altering this environment to prevent or arrest the cataractous and degenerative processes are additional foci of research activity. Deficits of antioxidant nutrients are under particular scrutiny in studies to clarify the etiology of cataract.
- Research is ongoing on the fundamental role played by essential minerals, such as zinc, calcium, and magnesium in lens metabolism and on the consequences for eye health of disturbances in mineral balances. The association between ascorbic acid levels in ocular fluids and the healing process after corneal trauma is also under investigation.
- Several studies are under way to detail the function of essential minerals which play a critical role in retinal function and in intraocular transport and function. The NEI also supports studies to determine whether dietary modifications may be effective in correcting the biochemical abnormalities associated with gyrate atrophy and other retinal degenerative diseases.

OUTLOOK

Among the eye and vision disorders addressed by the NEI, those with nutritional associations are perhaps the most easily prevented, diagnosed, and treated. In addition, the social relevance and international public health impact of these problems give them particular immediacy.

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NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

In 1966, the Secretary of the Department of Health, Education and Welfare established the Division of Environmental Health Sciences as a part of the NIH. The Division was elevated to institute status in 1969. To attack environmentally related health problems, the NIEHS supports a broad spectrum of biomedical research ranging from basic studies at the cellular and molecular levels to more applied programs aimed at identifying hazardous environmental substances and understanding both the effects from exposure to them and the mechanism by which they may cause biological damage. The Institute, which has its headquarters in Research Triangle Park, North Carolina, performs research in its intramural laboratories and through sponsored research throughout the United States and the world.

During the past year, the American public's concern over chemical contamination of our food and water supply has been at an all time high. Around the breakfast table, news headlines have included stories on pesticide residues in food supplies, contaminated drinking water, and cancer in fish.

Determining the identity and nature of these and other chemical, physical, and biological factors in the environment that may affect human health is at the core of NIEHS research. It also is reflected in the commitment of the institute to the National Toxicology Program (NTP), a DHHS interagency effort that attempts to fill information gaps about the possible toxicological effects of human exposure to environmental chemicals. Institute grantees and intramural scientists have utilized this extensive data base of scientific knowledge to facilitate their own research.

PROGRAM HIGHLIGHTS

In July 1989, NIEHS held a meeting on the toxicology and human health effects of methyl mercury, a compound found in many lakes that supply fish eaten by Americans. Consumption of methyl mercury contaminated fish presents a serious health risk, particularly to children and pregnant women.

As part of an effort to understand the mechanism of action of a class of insecticides, a grantee scientist discovered a new class of insecticides that have a higher selective toxicity for insects. Such highly selective chemicals could reduce the potential for human toxic effects through food-borne exposure to insecticide residues.

Institute grantees have used laboratory animals to show that chemicals transferred through breast milk can affect neonatal development of liver and reproductive function. In addition, it has been demonstrated that in adult laboratory animals certain agri-chemicals can contribute to reproductive dysfunction. These and other data suggest a role for agri-chemicals as contributing factors in human diseases.

Sensitive new assays have been developed for detection of the thiocarbamate herbicide, molinate, and the triazine herbicides, atrazine and simazine. These assays can be used to detect the presence of these chemicals in food products, and this technology has been transferred to the California Department of Food and Agriculture Chemistry Laboratory.

NIEHS held a conference in November 1989 on the implication for human health of possible changes in the global climate. Among the issues for consideration will be assessment of changes in the food supply. In a time of global warming, fungal contamination of grains and other stored foodstuffs is likely to increase dramatically.

Neurotoxicity was observed in lactating mice fed excess aluminum in a nutritionally marginal diet. In addition, decreased host resistance to bacterial infection was seen in maternal mice under optimal nutritional conditions. These results suggest that nutritional and reproductive/developmental status are important determinants of susceptibility to adverse effects of aluminum ingestion. Chlorine, a widely used disinfectant in water supplies, interacts with organic material in water to form a class of compounds having carcinogenic potential—the trihalomethanes.

For this reason there is increasing interest in substituting chloramine for water disinfection. However, the health effects of chloramine in water are currently ill-defined. NTP scientists are completing a chronic study of this compound in rodents to assess the safety of chloramine. Results of these studies will be vital to setting public policy on the desirability of increased use of chloramine.

An early finding from a study of 25 common groundwater contaminants indicated suppressed immune response in mice drinking the water. The mice appeared healthy, but were unusually susceptible to infections.

In an epidemiological study of 104 healthy women who had been attempting to become pregnant, it was found that women who consumed more than the equivalent of one cup of coffee a day were half as likely to become pregnant as were women who drank less coffee.

Conclusions from an NIEHS conference of experts, who met to discuss the problem of chemically contaminated aquatic food, indicate that certain kinds of water pollution are a likely cause of cancers and other diseases in fish. However, except for very fatty fish, the fish eliminate most of the carcinogens by the time they are ready to be eaten. Shellfish may be different as they often do not metabolize or get rid of pollutants, and a health risk may be posed from their consumption.

RESEARCH DIRECTIONS

NIEHS is exploring a number of areas that hold promise for furthering our understanding of the relationship between nutritional factors and human health. Selected examples include:

- In July 1990, the institute is holding a meeting to address a broad range of concerns which arise from the potential impacts on human health of the great volumes of chemicals used in agriculture, many of which become a part of the food sources.

- It is well-known that dietary restriction reduces spontaneous tumor incidence in animals. A study is under way to explore this relationship further to see if the incidence of chemically induced tumors can be reduced by limiting caloric intake.
- A project has been initiated to develop *in situ* a bioassay for assessing the bioavailability and bioaccumulation of toxic chemicals in the food chain.
- Sodium nitrite, a common food preservative, is found at elevated levels in the gastric juices of patients with precancerous gastric lesions. Additionally, populations with a high intake of nitrates and nitrites have increased risks of gastric cancer. These results are suggestive of an association between nitrites and cancer, but fall short of proof. A study is planned to determine the effects of sodium nitrite in a NIEHS/NTP prechronic test protocol.
- In order to establish/minimize the health risks resulting from exposure to hazardous substances, regulatory bodies require scientific data. A new project is planned that examines environmental substances that are potentially carcinogenic and are food-borne toxicants. The program will focus on carcinogens to which intermittent human exposure at low levels is virtually unavoidable and that have been established as risk factors for human cancers by epidemiologic studies.
- Monitoring and controlling for the presence in grain and food products of aflatoxin, a potent liver carcinogen, is hampered by difficulties in applying sophisticated analytical chemistry techniques in field settings. Through its small business program, NIEHS is developing sensitive devices for measuring this contaminant in the field.
- A number of studies examining breast milk as a source of chemical exposure are planned or under way. In Mexico, an NIEHS study is looking at the duration of lactation and illness of children exposed through mother's milk to DDE, a metabolite of DDT. An animal model is being developed for the

study of offspring exposure to drugs and other chemicals through mother's milk. In the course of this work, the drug cimetidine has been found in the milk of rats in concentrations 25 times higher than in plasma. The mechanism of concentration is still under investigation.

- Data analysis is under way in a study examining the biological response among a group of 70 postmenopausal women who have a diet high in plant estrogens.

OUTLOOK

The NIEHS is devoted to developing knowledge that will protect the environmental health of the world's population. In this connection, the institute's responsibility for nutritional research will continue to be an increasingly important part of the agenda.

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Today, approximately 12 percent of Americans are over age 65. By the year 2025, this number is expected to grow to over 20 percent as life span extends well into the eighth decade. The mission of the NIA is to foster research that finds methods to extend years of productive life through improved health, lifestyle, and psychosocial status. The NIA's Nutrition and Aging Program contributes to this goal by sponsoring basic, animal model, clinical, and population-based studies to determine the ways that nutrition influences the onset and progression of aging.

PROGRAM HIGHLIGHTS

Nutrition and aging research poses several unique challenges. The variation of physiological and behavioral measures increases with age. Because the rate of change in functional capacity and aging processes differs among individuals, those who reach old age are the most biologically heterogeneous of all age groups. The diversity observed in aging subjects results from a lifetime of environmental experiences superimposed on individual differences in genetic predisposition. Investigators in nutrition and aging must consider such factors as genetic variation, race, smoking status, physical activity, health and medication history, and social factors.

A most difficult problem is to separate those changes observed in old age that are due to inevitable aging processes from those that are manifestations of pathology. In some cases, like those related to the progressive loss of skeletal tissue, an aging process becomes pathological when bone density is reduced to a level where low trauma fractures can occur. Researchers also must determine if the magnitude of change in age-related parameters is clinically significant and which aging processes are detrimental to the health of older individuals.

Metabolic Studies in the Baltimore Longitudinal Study of Aging (BLSA)

NIA's Gerontology Research Center in Baltimore, Maryland, has been collecting

detailed nutrition information (7-day diet records) from male participants in the BLSA for almost 30 years. These data are being analyzed in relation to aging and development of various age-related diseases. Since 1984, 7-day diet records have been collected from women in the study.

Of the approximately 350 records collected from women, over 250 have been analyzed. An average of 45 percent carbohydrate, 16 percent protein, 35 percent fat, and 4 percent alcohol were consumed by the women. Cholesterol intake averaged about 280 mg/day. Over 50 percent of the women took some type of vitamin or mineral supplement, while only about 40 percent of the men took supplements. Older men were more likely to take supplements, but use did not vary with age in women. The basic diets of those taking supplements were more healthy than were diets of those not using supplements. Overall, diet alone provided inadequate intakes (less than two-thirds the RDA) of a number of vitamins and minerals for both men and women. Calcium intake declined with age in women. For vitamin B₆, calcium, iron, and magnesium, more women than men had lower than recommended intakes.

In conjunction with estimates of dietary intake, a number of biochemical measures of nutritional status are being analyzed. Plasma levels of antioxidant vitamins A and E were measured in about 1,000 subjects. Levels of a provitamin A, beta-carotene, were higher in women than in men, but levels increased with age in both sexes. Levels of preformed vitamin A, retinol, however, were higher in men and not related to supplement intake in either gender. Levels of tocopherol, the most active form of vitamin E, were higher in older people than in younger counterparts and were highest in those taking supplements. Plasma ascorbic acid levels were determined in about 400 men and women. Levels were higher in older people and higher in women than men. People taking vitamin C supplements had higher levels than those who did not, but increasing the amount of vitamin C supplements to megadose levels did not raise plasma levels. Ascorbic acid levels were correlated with a number of blood lipid

parameters. HDL₂-cholesterol, the fraction of HDL which is thought to protect against cardiovascular disease, was high in those with high ascorbic acid levels.

Because using a single 24-hour dietary recall is often not adequate to provide information on diet and health relationships, the BLSA group was used to pilot test telephone interview methods directed at collecting 24-hour computerized diet records. These approaches will be used to obtain additional dietary information for the third National Health and Nutrition Examination Survey (NHANES III). Sixty men and women were interviewed once in person and twice more in follow-up telephone interviews. Length of interview and number of foods reported were analyzed in relation to age and sex. Although the length of interviews decreased significantly after the first interview, no differences in the performance of men and women due to age were observed. The number of foods reported also remained constant between the in-person and telephone interviews. These data suggest the telephone dietary interviews will provide a useful adjunct to information collected from older people in the NHANES III.

Another study measured the efficacy of either normal or high protein, hypercaloric dietary intake on healing of pressure sores in nursing home patients. High protein diets were associated with better healing, especially if the patient had access to air-fluidized beds. Patients with pressure sores required a much higher caloric intake than those without this problem, although they were thinner and more anemic than other comparably diagnosed nursing home patients. These results show the need to maintain good nutritional status in this population.

In a different type of study, dietary intakes of senior athletes were compared to BLSA controls matched for age and body mass index (BMI). The athletes, ages 58-77, had a higher aerobic capacity and lower percent body fat than BLSA controls. They consumed more calories and protein per kg body weight and had a lower

percentage of calories from fat than the controls. These results suggest that habitual aerobic exercise can mediate changes in dietary intake and body composition associated with aging.

Some promising research areas for the 1990's include antioxidant vitamin levels and macular degeneration and cataract formation; B vitamin status and cognitive function changes; and sulphur amino acid levels and atherosclerosis.

Nutrient Requirements in Older People

In order to understand how nutrition supports good health and helps to maintain function in old age, it is important to identify the ways nutrients may influence tissues and organ systems. Also, the question arises as to what relationships exist between dietary components and age-related diseases. Despite a paucity of information regarding the age specific nutritional requirements of older people, significant progress is being made in a number of nutrition and aging research studies, including those investigating the absorption and metabolism of lipids. In animal models, aging is associated with increased intestinal capacity to absorb lipids, notably vitamins A, D, and E, and mono- and polyunsaturated fatty acids.

The unstirred water layer (UWL) in the small intestine helps control the absorption rate of lipids. The greater surface area and thinner water layer that occurs with age decreases the resistance to lipid absorption. Based mainly on animal studies, some investigators hypothesize that this age-related increase in intestinal absorption of fats may be an adaption of the bowel to decreased pancreatic and hepatic digestive function. Protein and carbohydrate absorption that are not regulated by the UWL do not increase with age.

Lipids are absorbed by passive diffusion with rapid accumulation of triglycerides by brush border membranes and the lumen of the vesicles. Vitamin E absorption shifts from

portal to lymphatic transport with age. Although vitamin D transport does not appear to be compromised during the aging process, some older people have a lower vitamin D status. Older women, who are at highest risk, have a higher potential for urinary calcium loss, lower serum levels of 25-hydroxy vitamin D, and a lower potential for synthesizing vitamin D, due in part to less exposure to sunlight. These are factors that may contribute to the higher incidence of osteoporosis in older women.

Nutritional Status in Older People

Except for certain subgroups such as the economically disadvantaged and chronic alcoholics, epidemiologic evidence indicates that clinical undernutrition is uncommon in the majority of free-living older people in the United States (less than 5 percent of NHANES subjects over 50 years). Although the majority of older people are not undernourished, they represent a particularly vulnerable segment of the population. Studies have shown that even in the absence of clinical deficiency symptoms, the average serum levels of some nutrients such as vitamin D and folate are lower in older age groups than in younger persons (less than 50 years of age). These differences may be responsible for subclinical deficiencies or reduced body stores that increase their vulnerability to intercurrent illness or to the chronic diseases of old age.

Recent evidence also suggests that age-related changes in body composition are related to nutritional and health status of older people. In many mammalian species, there is a loss of lean body mass and a decrease in total body water accompanying an increase in body fat. This proportional change from lean body mass to fat can change the basal metabolic rate, lowering the need for energy. These changes involve alterations in hormonal control and in complex metabolic regulatory systems. In humans, adipose tissue increasingly tends to distribute in the trunk and around vital organs. In women, there appears to be a post-menopausal acceleration of this trend but the waist-hip ratio is distinctly higher in men.

The sex difference in waist to hip ratio is due to differences in waist circumference; changes in women occur in both the hip and the waist while in men the waist changes but hip size remains about the same. Overall, BMI and waist-hip ratio are highly correlated.

Using BMI as a measure of obesity, mortality in older people increases at both the low and high end of the scale with an upward shift in optimal BMI with age. Longitudinal studies show that over a period of 10 years, in those 55 to 74 years at baseline, male mortality decreased with increasing BMI except for the morbidly obese. No such association was found in women. These data were adjusted for the effects of related factors such as blood pressure, smoking, socioeconomic status, and diabetes. In cross-sectional analysis, male smokers weigh less and have a lower BMI than nonsmokers. Male smokers also have a significantly higher waist-hip ratio than nonsmokers. Those who begin smoking lose weight but increase their waist-hip ratio, enhancing their health risk.

Severe signs of malnutrition are apparent in many older persons requiring hospitalization and/or the services of long-term care facilities. There is increasing recognition of a syndrome in this group of unexplained rapid weight loss and emaciation, usually associated with an unexplained decrease in food intake. This cluster of symptoms has the characteristics of protein-calorie malnutrition (PCM). PCM is being diagnosed more frequently among hospital patients, especially in the oldest age groups. The incidence of PCM among those 65 years and older is between one-third and two-thirds of those admitted to acute care facilities. Furthermore, the rate of malnutrition increases with the length of stay. The NIA is encouraging further research on the pathogenesis of this form of PCM to determine whether it represents a syndrome in its own right or occurs secondary to disease.

Energy Restriction in Animals—A Probe into Mechanisms of Aging

In rodents, energy intake restriction without essential nutrient deficiency extends maximum

life span, retards the onset of many spontaneous late-life diseases, and slows the rate of biological aging. Because caloric restriction has been the only intervention that has consistently produced these outcomes, investigators in several areas of basic biology such as peroxidation/free radicals and intermediary metabolism are using this model to test hypotheses about basic mechanisms of aging. Linking energy restriction to longevity may include changes in energy metabolism, gene expression, neuroendocrine regulation, and immune function. Another issue to be resolved is whether this effect seen in rodents and several other animal models applies to primates.

A project at the Baltimore GRC is attempting to determine whether a 30 percent calorie reduction in the ad libitum diet of rhesus and squirrel monkeys can affect the aging rate of a number of physiological, biochemical, and behavioral systems. Two years into the study, preliminary analysis indicates measurable changes in the restricted rhesus monkey compared to the ad libitum controls of similar age. Most notable of these are changes in indices of bone remodeling, albumin levels, and globulin ratios. Age-related decreases in concentrations of lymphocytes and several enzyme levels were observed in the calorie-reduced animals of both monkey species.

Age-related Changes in the Chemical Senses

With increasing concern about the nutrition status of older people has come an increased interest in changes in their chemosensory function. According to recent evidence from anatomic, electrophysiologic, and psychosocial studies, both taste and smell decline with age.

For example, psychophysical studies of the gustatory system have demonstrated age-related elevation in the threshold of some, but not all, taste and smell stimuli. The role of this change in an individual's perception of real-world foodstuffs is a matter of current speculation. More than half the population over age 65 show some degree of impairment of

odor recognition. Furthermore chemosensory preference for foods that may have different nutrient patterns from those preferred at a younger age, raises the question of a possible relationship between nutritional and chemosensory status.

Osteoporosis and Aging

The risk of low-trauma fracture increases with age because of the almost universal loss of bone mineral that occurs throughout the life span. As bone is lost, increasing numbers of older people have bone densities that fall below a fracture threshold. By this definition, most women will be osteoporotic by the time they are 75 years old.

Clinical evidence and differences in age-specific fracture rates suggest that there may be two primary types of osteoporosis. Type I (designated as estrogen dependent) occurs mainly in women up to 20 years after menopause and is manifested by crush fractures of the spine and fractures of the wrist and forearm. Type II (age dependent) occurs in both men and women over the age of 70 and is associated mainly with hip, pelvic, upper femur, and wedge-type spine fractures.

The marked differences in regional bone loss with age indicate that architectural changes also are taking place. The type II form of osteoporosis is characterized by a proportional loss of cortical and trabecular bone while Type I is associated with a disproportionate loss of trabecular tissue. The differential loss of trabecular and cortical bone influences the type of fracture which occurs. NIA researchers are trying to find ways to prevent and treat both types of osteoporosis with special emphasis on the age related syndrome.

Some modifiers of bone loss have nutritional implications. Type II risk factors include decreased osteoblast function and impaired 1,25 dihydroxy D, leading to decreased calcium absorption and secondary hyperparathyroidism. New evidence indicates that older women have an increase in bone turnover due to

the secondary hyperthyroidism incident to old age. It is hypothesized that an increase in calcium would prevent an increase of parathyroid hormone (PTH) secretion which leads to an increase in bone turnover.

Although relatively safe and inexpensive, calcium supplements have not proved to be as effective as hoped in preventing or slowing bone loss in postmenopausal women. However, when a group of osteoporotic elderly women were supplemented with 1,500 mg of calcium per day the results were more favorable. Untreated women continued to lose vertebral bone, but the supplemented group had a significant increase in bone mass density over the 4-year trial period.

Vitamin D also may prove to be a valuable adjunct to osteoporosis therapy for older people. It stimulates the osteoblast *in vitro* and *in vivo* to produce osteocalcin which makes it likely that vitamin D therapy can promote bone gain in older people. In a prospective trial of 15,000 IU per week of oral vitamin D versus a placebo given to a group of women ages 65 to 74, the supplemented group showed an increase in serum calcidiol and a significant increase in the metacarpal cortical width and area. In addition, vitamin D is used successfully to treat proximal myopathy, a common occurrence in vitamin D deficiency. New studies are examining the effect of vitamin D on muscle strength in older subjects with vitamin D insufficiency and its relation to falls.

In addition to current research priorities, new directions will include research designed to discover therapeutic agents that promote normal bone growth as well as reduce bone loss and identify risk factors that cause falls in older people.

RESEARCH DIRECTIONS

The NIA is continuing its efforts to expand the Nutrition and Aging Program. A key task in the expansion plans was to develop a rationale for research priorities. The NIA solicits input from the scientific community to aid in

identifying the most important topic areas and directions for nutrition and aging research.

Present research directions and areas of research priority in nutrition and aging are based on NIA staff evaluation of current research, advice from scientific advisors, and the results and recommendations from the nutrition and aging conferences. These include:

- Nutrient requirements and their age-dependent changes in older persons and animal models.
- Effects of age on physiological processes through which nutrients, drugs, and other non-nutrient substances are absorbed, metabolized, and excreted in humans and in analogous animal models.
- Effects of calorie reduction and of caloric excess resulting in obesity on longevity and age-related pathology.
- Nutritional factors associated with physiologic changes such as immunocompetence, neurologic function, body composition, sensory perception, control of appetite, macronutrient storage and utilization, rheology, and otolaryngology, endocrine control, and genetics.
- The role of nutrition factors in prevention and treatment of age-related degenerative diseases, including diabetes, osteoporosis, neurologic disorders, immune deficits, heart disease, cancer, and gastrointestinal diseases.
- Psychosocial aspects of nutrition, including studies of diet as a major factor contributing to the quality of life and how diet interacts with other lifestyle variables, including exercise, smoking, and consumption of alcoholic beverages.
- Nutritional status of older Americans and special subpopulations of older people at special nutritional risk.
- Educational methods and program strategies that best promote adequate food consumption by older people.

OUTLOOK

A rapidly aging population makes it critical to find ways to maximize the span of good health

and thereby improve the quality of life of older people. Nutritional factors hold great promise for realizing this goal. For these reasons, NIA's Nutrition Program supports research to clarify nutrition-aging interactions.

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NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

In 1950, major arthritis research programs were established within the National Institute of Arthritis and Metabolic Diseases through the Omnibus Medical Research Act. The research programs of the Institute evolved over the decades, and its name eventually became the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) in 1980. The Health Research Extension Act of 1985 re-established the programs of the NIADDK as two institutes: the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institute of Diabetes and Digestive and Kidney Diseases.

The NIAMS conducts and supports basic and clinical research on many of the most debilitating diseases affecting the U.S. population. These include the many forms of arthritis and numerous diseases of the musculoskeletal system and the skin, as well as research on the normal structure and function of joints, muscles, bones, and skin. Basic research involves a wide variety of scientific disciplines, including immunology, genetics, molecular biology, biochemistry, physiology, virology, and pharmacology. Clinical research addresses the fields of rheumatology, orthopedics, bone endocrinology, sports medicine, and dermatology. The NIAMS supports nutrition research related to these disease areas, scientific disciplines, and clinical fields.

PROGRAM HIGHLIGHTS

Current nutrition-related research efforts include examination of associations between diet and bone mass, osteoporosis, and fractures, especially the identification of nutritional factors that may prevent or slow the progression of osteoporosis, the role of omega-3 fatty acids in rheumatic and skin diseases, and the study of the treatment of various skin conditions with vitamin A derivatives.

Osteoporosis and Nutrition Research

Osteoporosis, characterized by severe bone loss and an increased risk of fracture, affects an estimated 24 million Americans and causes approximately 1.3 million fractures per year among those 45 or older. The NIAMS has several research efforts under way that focus on the etiology, treatment, and prevention of osteoporosis, including the nutritional aspects of this major public health problem.

Osteoporosis may be classified into primary and secondary forms. Primary (or involutional) osteoporosis may occur in two types: type I, which occurs in women when estrogen levels decline after menopause; and type II, which is the inevitable loss of bone mass that occurs in both men and women with increasing age. Secondary osteoporosis may develop at any age as a consequence of endocrinologic, gastrointestinal, or metabolic disorders.

The NIH has sponsored major conferences in 1984, 1987, and 1990 to summarize the research advances in osteoporosis. Nevertheless, the nutritional controls of bone mineralization have yet to be identified fully. At present, the only established nutritional determinants of bone mineralization are calcium, phosphate, and vitamin D.

Primary prevention of osteoporosis begins in adolescence and the early adult years when the skeleton is accruing its genetically programmed peak bone mass. Nutritional deficiency, particularly of calcium, at that time may result in a permanent skeletal deficit. In recognition of both the importance of the period of growth and the fact that bone consolidation continues into the third decade, the National Research Council recently extended the adolescent Recommended Dietary Allowance for calcium (1,200 mg) through age 24 years.

Secondary prevention involves helping preserve skeletal mass accumulated at

maturity. Postmenopausal estrogen therapy is the primary method for preventing bone loss and fractures in women. However, recent evidence indicates that high calcium intakes (1,500 mg/day) by postmenopausal women may reduce hip fractures by as much as 60 percent. More studies are needed on the role of dietary calcium in adult premenopausal women and elderly men and women.

Significant advances in assessing bone mass and density by noninvasive methods have enhanced the diagnosis and monitoring of osteoporosis. These improved methods, which include dual-photon absorptiometry, computerized tomography, and dual-energy x-ray absorptiometry, will aid in monitoring the efficacy of nutritional supplementation.

Intestinal Absorption and Bioavailability of Calcium

Alterations in calcium absorption contribute to abnormal mineral metabolism in metabolic bone disease. The management of patients with these disorders would be improved if clinically useful measures of calcium absorption were available. Calcium absorption can be quantitated by the balance method or by double isotope techniques. True fractional calcium absorption, assessed by the balance method, is based on the proportion of the dietary calcium intake measured in total stool collections with appropriate corrections for recovery and endogenous stool calcium. Although this method is highly accurate, it is very labor intensive and requires admission of patients to a metabolic unit for one to two weeks.

Absorption also can be measured by labeling dietary calcium with ^{47}Ca and then injecting ^{45}Ca intravenously. Fractional absorption is the quotient of the two tracers in samples of pool calcium relative to the administered dose. This is usually followed by making measurements of serum and urine calcium radioactivity over several days to achieve an equilibrium value. While both of these methods have proven useful for clinical research, they have not been generally applicable to patient management. The balance method is very time consuming, and

the use of the isotopic method is limited because of radiation exposure concerns.

A recent, long-term study by NIAMS grantees using both the balance and isotopic techniques has confirmed that calcium absorption is inversely related to calcium intake and, moreover, is dependent on estrogen status and age. This study followed a cohort of women for 17 years, making multiple measurements of calcium absorption on each woman, providing information about the degree of individual variation in calcium absorption in a free-living white female population.

A new and potentially useful measure of calcium absorption in patients may provide an economically and technically feasible method to identify individual low and high calcium absorbers. This method uses stable isotopes of calcium administered with the subject's usual diet and then measured by mass spectrometry in a 24-hour urine collection. The true fractional calcium absorption calculated from stable isotope absorption correlated well with a 7-day balance study. The advantages of this new method are avoiding exposure to radioisotopes (permitting extension of balance studies to pregnant women and children), improving precision, and lowering cost compared to radioisotope methods. Currently, the limited availability of the mass spectrometry may limit its utilization.

Interindividual variation in calcium absorption appears to account for most of the variability observed in healthy volunteers. Future research will focus on the factors responsible for this variability but it now seems possible to begin to apply new methodology to patients with metabolic bone disease or those at high risk. Prescribing calcium supplements or otherwise modifying calcium intake can begin to have a more rational basis.

There is general agreement that the best natural source of calcium is dairy products, where the bioavailability—the amount of calcium absorbed and used by the body—is established. Scientists recently have measured the absorption of calcium from kale. In contrast

to the poor absorption of calcium previously reported from spinach, kale, a low oxalate vegetable, exhibits excellent calcium absorbability—in fact, slightly better than milk.

Fluoride Effects on Bone

The ideal therapy for osteoporosis would restore lost bone and correct alterations in architecture that contribute to fractures. Current treatments such as estrogen and calcitonin only prevent further bone loss. Several studies have indicated that sodium fluoride can contribute to the restoration of bone mass, and it has been used extensively in Europe to treat osteoporosis. Until recently, there had been no well controlled clinical trials of the effects of fluoride in women with post menopausal osteoporosis using fracture frequency as an end point. The results of two placebo-controlled, double-blind studies were announced this year and confirmed that sodium fluoride supplementation (75 mg/day) increased bone mass.

However, both studies failed to establish any efficacy of fluoride in fracture reduction. In spite of these disappointing results, fluoride does have the capacity to induce bone formation. Further investigation of the basic mechanism of fluoride action on bone is clearly warranted. Some possibilities for future clinical investigations include trials with different formulations and dosages of fluoride, as well as a study of whether the addition of fluoride to standard antiresorption regimens can be beneficial.

Vitamin D and Bone

The active metabolite of vitamin D₃, 1,25-dihydroxy vitamin D₃, is highly effective in regulating the absorption of calcium from the intestine and has a strong influence on the metabolism of bone cells. The receptors for this active agent are intracellular polypeptides. The human vitamin D receptor has recently been cloned and sequenced by NIAMS supported investigators. The full nucleotide sequence shows similarity with other steroid hormone receptors and thyroid hormone receptors. These

studies support a hypothesis that the mechanism of vitamin D action involves interaction of the receptor-bound active agent with nucleotide sequences in the nucleus of the target cells, paralleling the action of steroid hormone receptors. Advances in the cloning and sequencing of the human vitamin D receptor provide an opportunity for enhanced functional studies of vitamin D activity in target cells. One area of particular interest will be examination of aberrant receptors found in vitamin D-dependent rickets.

Lactation and Bone

Lactation increases the dietary calcium requirement and has the potential to affect bone mass and future fracture risk. Since periods of lactation may coincide with the time of the achievement of peak bone mass, between the ages of 20 to 35 years, it is important to evaluate any changes in bone mass during this period and to determine if they are related to age, diet, degree of lactation, or body composition. An ongoing study will assess biomedical measures of bone turnover as well as bone mass in women who are breast or bottle feeding. These studies will provide needed information on the impact of women's reproductive lives on their future risk of osteoporosis.

Vitamin A and Retinoid Effects on the Skin

Vitamin A and retinoid effects on the skin continue to be an active area of research. Retinoids are regulators of the differentiation process in epidermis. Basic studies are under way to determine the role of vitamin A in the expression of the genes for keratin proteins in epithelial cells. These functionally important proteins play a role in the normal development of skin cells and possibly in the development of skin cancers.

Clinically, pharmacologic doses of vitamin A or other retinoids have been used to treat conditions such as acne, psoriasis, and some forms of skin cancer. Basic research on the mechanisms of action of these agents is being

supported toward the development of additional clinical applications.

Omega-3 Fatty Acids

Evidence that polyunsaturated fatty acids, particularly omega-3 fatty acids, and their oxidative derivatives can affect immune function and inflammatory reaction, has led to interest in the effect of dietary supplementation on a variety of chronic diseases including rheumatoid arthritis, systemic lupus erythematosus, and psoriasis. These fatty acids are found in high concentrations in the lipids of marine animals. If added to the diet, omega-3 fatty acids incorporate into cellular membranes throughout the organism, substituting for arachadonic acid. The metabolism of membrane-bound arachadonic acid leads to two major classes of bioactive products, the prostaglandins and the leukotrienes. The oxidative derivatives of arachadonic acid actively enhance synovial cell proliferation in the inflamed joint. Substituting omega-3 fatty acids for arachadonic acid may decrease the production of prostaglandins and leukotrienes, or substituting the production of less active compounds by enhancing the diet with sources of omega-3 fatty acids, could provide a useful, specific, and potentially nontoxic mechanism for controlling joint inflammation.

Several research projects are currently directed toward the role of omega-3 fatty acids in the pathogenesis of rheumatoid arthritis. Proliferation of synovial cells is a hallmark of rheumatoid arthritis and a central event leading to joint injury.

Dietary manipulation of fatty acid composition also may have therapeutic potential in inflammatory skin diseases. Epidemiologic studies point to a decreased incidence of skin disease in fish eating populations but the agents responsible and the mechanisms involved have yet to be elucidated. Both prostaglandins and leukotrienes have been shown to play important roles in the

pathogenesis of some skin disorders, such as psoriasis.

Studies have indicated that another polyunsaturated fatty acid, gammalinolenic acid (20:3n-6), in evening primrose oil exerts a beneficial effect on inflammatory skin disorders, such as atopic eczema. A recent study indicates that the beneficial effects of some polyunsaturated fatty acids may be due to the production of specific anti-inflammatory metabolites in epidermal cells. Ongoing studies will determine both the mechanism of action of omega-3 fatty acids and other polyunsaturated fatty acids on inflammatory skin disorders, as well as the spectrum of possible therapeutic uses.

RESEARCH DIRECTIONS

The NIAMS supports programs of research and research training in the fields of arthritis, musculoskeletal diseases, muscle biology and skin diseases. Examples of ongoing nutrition research supported by the NIAMS are as follows:

- Studies to determine the optimal intake of calcium and the role of exercise in the development and maintenance of strong, healthy bones; for attaining a maximum adult peak bone mass; for minimizing the rate of bone loss in older individuals; and for the prevention of osteoporosis.
- Assessment of calcium absorption in women and its relationship to calcium intake, estrogen status, and age.
- Evaluation of bone density in patients with anorexia nervosa and determination of the extent to which recovery of bone density is possible in young adults.
- Research to determine the role of vitamin D metabolism in the pathogenesis of the vitamin D refractory diseases.
- Studies of the direct effects of vitamin D on bone cells in culture.
- Investigation of the effects of fluoride on the cellular and matrix components of bone.
- Research on the effects of omega-3 fatty

acids, administered as fish oil supplements, on the pathogenesis of rheumatoid arthritis and other diseases characterized by chronic inflammation.

- Investigations to determine the functional relationship between essential fatty acid deficiency and skin conditions, such as abnormalities of desquamation (normal loss of bits of outer skin in scales) and defects in the skin's water barrier.
- Research on the mechanism of action and possible therapeutic uses of vitamin A and its synthetic derivatives, the retinoids, in skin biology.
- Studies of the effect of fatty acids and lipid metabolism on the differentiation of keratinocytes (skin basal cells).
- Studies of the effects of aluminum on bone formation and osteoporosis.
- Research on the photobiology of vitamin D.
- Support of arthritis, osteoporosis, and skin disease aspects of the Third National Health and Nutrition Examination Survey through an interagency agreement with the National Center for Health Statistics.

OUTLOOK

The institute's programs are organized to respond to public health needs as well as to the research opportunities and needs identified by working scientists in the academic community.

The NIAMS also enjoys a strong partnership with several private voluntary agencies dedicated to the control of relevant diseases. The concerted national effort that these forces bring into play will ensure continued progress toward more effective methods of treating and perhaps preventing these chronic diseases.

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NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS

In October 1988, the NIDCD became the 13th institute mandated by Congress within the NIH. The NIDCD conducts and supports research and training on normal mechanisms as well as disorders of hearing and other communication processes, including diseases affecting hearing, balance, smell, taste, voice, speech and language. NIDCD achieves its mission through a wide range of research performed in its own laboratories, a program of research grants, individual and institutional research training awards, career development awards, center grants, and contracts to public and private research institutions and organizations. The institute also conducts and supports research and training that is related to disease prevention and health promotion. NIDCD addresses special biomedical and behavioral problems associated with people who have communication impairments or disorders. The legislation that established NIDCD also directed that the Institute establish the NIDCD National Information Clearinghouse to collect and disseminate information to health professionals, patients, industry, and the public on research findings related to deafness and other communication disorders.

Nutrition-related research is a component of the NIDCD chemical senses programs. The chemosensory programs are supported through a variety of funding mechanisms, including program project and center grants. The Congressional mandate for the NIDCD chemosensory program includes the establishment of a data system derived from patient populations with disorders of smell and taste, including, where possible, data involving general populations for the purpose of identifying individuals at risk of developing those disorders. In addition, the NIDCD Information Clearinghouse will include the dissemination of information on nutrition/chemosensory disorders to facilitate and enhance knowledge and understanding of nutrition-chemosensory disorders by health professionals, patients, industry, and the public.

PROGRAM HIGHLIGHTS

What is ingested and rejected depends largely on its smell and taste. Ingestive choices can influence various disease states such as hypertension and metabolic disorders. In turn, these disease states can affect chemosensory function and nutrient intake. Nutrition factors may serve as independent or dependent variables in studies of chemosensory function at levels of organization from reception to perception and behavior. For example, research may focus on the effects of sodium chloride (NaCl) on the ion channels of taste cells or on the effects of chemosensory status on NaCl intake.

Chemosensory Disorders and Dietary Intake

Some individuals suffer from distorted smell or taste sensation or from the chronic presence of unpleasant smells and tastes in the absence of obvious stimulation. These chemosensory disorders can make eating extremely unpleasant. Recent preliminary research conducted at a chemosensory center indicates that these patients tend to decrease food intake and lose weight after the onset of their chemosensory problem, whereas patients with loss of chemosensory function tend to increase food intake and gain weight. Many of the patients reported alterations in food cravings in their salt and sugar intake after the onset of their chemosensory problem.

In another study patients with both distorted taste and the burning mouth syndrome are being examined to determine the role of mineral and vitamin deficiencies in their disorders.

Age and Olfaction: International Survey

With the assistance of NIDCD-supported scientists, the National Geographic Society conducted a massive international smell survey. Over one million readers of the *National*

Geographic magazine completed the survey. The results confirmed previous surveys, showing that smell perception declined with age. However, this decline was not uniform across subjects, odorants, or measures of perceptual responses such as pleasantness ratings. The ability to detect the smell of six samples of microencapsulated odorants varied across age in odorant-specific fashion. For example, large changes were noted in the ability to detect the smell of the steroid adrostenone, but the likelihood of smelling rose was quite high, at least until the eighth or ninth decade. The ability to smell adrostenone declined steadily from the second decade on. The ability to smell rose began to decline in the sixth decade. The pleasantness rating of the odorants also was affected by age. In future years it may be possible to incorporate smell or taste tests in well-controlled nutritional surveys.

Salt Taste Reception and Perception

The taste system is the primary sensory system that regulates salt intake, which is a crucial component in the homeostatic control of sodium levels. Important progress has been made in understanding the molecular and cellular aspects of salt taste perception. Converging evidence indicates that a voltage-independent sodium channel, which is blocked by amiloride, mediates at least some components of sodium taste. Developmental studies demonstrate that taste cell receptors have an early, low sensitivity to sodium and gradually acquire increasing responsiveness. Other investigations suggest that taste receptors acquire this sodium sensitivity by adding specific membrane components that can be blocked by amiloride. For example, sodium ion channels may be added during development. Acquisition of this membrane component apparently can be blocked by dietary salt deprivation during early developmental periods in animal models. Aldosterone or other hormones may play an important role in regulation of the sodium receptor components in the taste bud. If applicable to taste, such hormonal mechanisms would unify regulation of sodium taste receptors

with regulation of sodium in cells throughout the body. Sodium taste receptors might be regulated relatively rapidly in response to diet changes, changes in salivary composition, or plasma electrolyte levels. Thus, the taste system could alter intake appropriately to maintain sodium homeostasis.

The demonstration of a progressively emerging, environmentally susceptible sodium taste system appears to be reflected in the perception of salts in humans and in other mammals. As predicted from functional responses, rats seem capable of responding behaviorally to some taste stimuli soon after birth. However, their responsiveness to salts changes dramatically during a prolonged period of development. For example, 5-day-old rats show no evidence of a preference for NaCl solutions over water, regardless of the NaCl concentration. Mature preferences and aversions for NaCl do not occur until much later in the rat's development. Premature and full-term human newborns discriminate among taste stimuli and exhibit affective responses to acids, sugars, and some bitter stimuli. However, it has been difficult to demonstrate that the human newborn can detect and respond to NaCl. Recent observations from developmental studies indicate that mature behavioral responses to NaCl are not expressed until about 4 years of age.

The experiments on salt taste sensation and how salt taste develops can contribute to understanding changing salt preference and the importance of prevention of excess salt intake in infants and children. High salt intake in humans has been implicated in the development and maintenance of hypertension.

Dietary Sodium and Early Development of Sodium Taste

Early and continued restriction of dietary sodium in pregnant rats and their pups reduced the neurophysiological response of a peripheral taste nerve branch, the chorda tympani, to NaCl in the pups without altering responses to KCl and NH₄Cl. Amiloride did not suppress the sodium taste responses. These

effects were not permanent. Normal neurophysiological responses to sodium salts were restored when the pups were fed a normal sodium diet, and amiloride-induced suppression of the sodium response was restored. However, the dietary sodium restriction produced permanent alterations in the taste system upstream from the taste receptor cells as indicated by behavioral responses and physiological and anatomical alterations in the central nervous system. The rats consumed less salt solution than control counterparts in a two-bottle preference test and avoided a NaCl-based cue less than controls in a conditioned aversion test. The responses from the brainstem target of the taste nerve were different from controls, and the projection area in the nerve target was greater than in controls.

Molecular Biology of Sweet Proteins

Intensely sweet proteins such as monellin and thaumatin have some interesting characteristics. They are low in calories, safe, natural, and neither introduce unnatural metabolites into the body nor perturb the balance of the amino acid pool. One of the limitations in the use of these compounds as sweeteners is their poor heat stability. Cross-adaptation and electrophysiological studies suggest that the two proteins are recognized by the same receptor. Using crystallography, nuclear magnetic resonance, and genetic engineering techniques, NIDCD-supported investigators are redesigning monellin to improve its heat stability and other physical characteristics and to facilitate site-directed mutagenesis for determining the receptor recognition site. A synthetically fused monellin has been created and is being used as a tool to identify that part of the protein which is recognized by the sweet receptor.

RESEARCH DIRECTIONS

Examples of nutrition research supported within the fields of the chemical senses are as follows:

Human Studies

- Evaluate the association between nutritional status and problems of the senses of taste and smell in order to develop effective preventive interventions for individuals with various diseases.
- Study the relations between food intake, hormone levels, and taste sensitivity in pregnant women and their infants.
- Determine whether providing premature, tube-fed infants with sweet taste stimulation during feeding enhances growth and allows earlier progression to oral feeding.
- Identify the chemosensory disorders underlying inadequate food intake and complaints about bad tastes of certain foods by individuals with liver disease.
- Determine the efficacy of the drug tetrahydrocannabinol in stimulating appetite in healthy persons and in persons with diseases such as cancer.
- Study the contributions of oral trigeminal sensation to taste and the perception of flavor.
- Determine the degree to which the genetically determined variation in taste sensitivity to phenylthiocarbamide and related chemicals is correlated with taste sensitivity and hedonic responses to foods and beverages containing sweet and bitter components.
- Study the genetically determined variation in the sensitivity and hedonic responses to the smell of androstenone, a natural steroid in bacon, celery, and truffles.

Animal and Other Basic Research

- Determine whether salt appetite or the renal response following mineral corticoid administration to spontaneously hypertensive rats are related phenomena and if so, due to the same natriuretic mechanism.
- Study the changes in ingestive behavior after damage to specific parts of the taste system in the hindbrain.
- Determine whether the hypothalamic regions modulating conditioned food aversions are similar to those attenuating cancer anorexia.

- Assess phenotypic differences in aversions to bitter substances in inbred strains of mice using behavioral, physiological, and molecular techniques.
- Elucidate the emergence of sodium chloride preference in a salt glutton strain of young rats and in a strain with a distaste of salt to determine whether their preferences are due to differences in amiloride-sensitive sodium transport in taste buds.
- Determine the mixture interaction effects of different tastants and olfactants in behavioral and neurophysiological studies.
- Determine the 3-dimensional structure of intensely sweet proteins with x-ray crystallography to understand the molecular basis for sweet taste and thereby facilitate the rational synthesis of more effective sweet proteins.

OUTLOOK

Because nutrition often is a biomedically significant factor in studies of smell and taste, the NIDCD will continue to support nutrition/chemosensory research in the smell and taste programs. Because this research often is of trans-NIH relevance the NIDCD will continue to collaborate with other components of the NIH. This outlook reflects the recommendations of a Task Force of eminent scientists who formulated the National Strategic Research Plan of the National Institute on Deafness and Other Communication Disorders in January 1989.

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NATIONAL CENTER FOR NURSING RESEARCH

The NCNR, established in April 1986 as an NIH component, supports research in nutrition as it relates to health promotion, disease prevention, and acute and chronic illness and disabilities. The goal of nursing research is to improve nursing care for all segments of society by expanding the scientific base for nursing practice, focusing on the full spectrum of human health and disease, from the prenatal stage to old age.

PROGRAM HIGHLIGHTS

Although behavioral nutrition is not the primary focus in most of the nutrition-related studies at NCNR, investigators collect data on nutritional intake and behaviors affecting the utilization and intake of nutrients. Current NCNR nutrition highlights are primarily in infant health, in health promotion, obesity, and human immunodeficiency virus (HIV) infection.

Infant Health

The nutritional implications for infants begin with the nutritional health of their mothers prior to birth. One NCNR study is directed toward identifying maternal health behaviors during pregnancy as they relate to pregnancy outcome. Two other studies follow the growth and development of infants after birth and measure their nutrition status.

Health Promotion

Nutrition is one of a number of health promotion behaviors being examined in a variety of populations. A group of adolescents is being studied to identify health compromising behaviors, including poor nutritional habits. Adults at risk for health problems such as cardiovascular disease and skin breakdown, which would include ulcers or lesions, are being studied to identify the nutritional behaviors related to health status.

The impact of nutrition on premenstrual symptoms in women also is being examined.

Obesity

Many obese Americans face curtailed life expectancy and the prospect of developing a major disabling or fatal disease. The NCNR is supporting studies that examine the genetic, metabolic, clinical, environmental, and behavioral aspects of obesity in animal models; define types of obesity; and establish better methods of prevention and treatment. Recent studies on weight gain after weight loss have led to new information on the complex interactions of the body's systems controlling energy intake and energy expenditure. The NCNR is supporting research on behavioral patterns conducive to weight control by testing the effectiveness of self-management strategies.

HIV Infection

Nutritional alterations occur commonly during infections such as HIV, either as a direct consequence of the disease process itself or as a result of therapies. Studies are under development by NCNR that will examine different aspects of nutrition during HIV and its treatment, including:

- 1) exploring the nature and extent of nutritional problems;
- 2) examining the etiology of nutritional changes;
- 3) evaluating changes in body composition that occur during HIV infection;
- 4) assessing the relationship between nutritional status and immune infection; and
- 5) analyzing the indications for and effectiveness of nutritional interventions.

RESEARCH DIRECTIONS

The NCNR has developed the research structure needed to make progress in priority areas that address specific health concerns of

society. The nursing research priority areas with nutrition research potential include:

- Improved feeding techniques for low-birth-weight infants to provide needed nutrition and support weight gain.
- Assessment of nutritional needs and related issues in elderly persons who require long-term care.

OUTLOOK

The challenge that lies ahead for NCNR is to encourage a strong research environment that will produce the scientific knowledge needed to guide nursing practice. Future studies will build on the basic sciences, integrating them with the biological, behavioral, and social correlates that influence nutritional health and disease. Collaboration with other NIH components is of continuing importance.

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JOHN E. FOGARTY INTERNATIONAL CENTER FOR ADVANCED STUDY IN THE HEALTH SCIENCES

Established in 1968, the FIC supports fellowships to enable U.S. and foreign scientists to pursue their research interests in U.S. and foreign laboratories, providing an opportunity for them to exchange information and research experiences.

There are three distinct fellowship programs:

The Senior International Fellowship (SIF) Program is intended to enhance the exchange of ideas and information about the latest advances in the health sciences and to improve the research, educational, and clinical potential of the U.S. nominating institutions. These U.S. scientists spend from 3 to 12 months in foreign laboratories pursuing projects of mutual interest to the fellows and the foreign host scientists. Between 30-40 awards are made annually.

The International Research Fellowship (IRF) Program was established to stimulate health-related research by enabling foreign postdoctoral biomedical or behavioral scientists to extend their research experience by working with distinguished U.S. scientists on problems of mutual interest. About 100 awards are made each year to foreign scientist who are in the formative phase of their research career. Approximately two-thirds of the fellows receive 2-year awards.

The Foreign-Funded Fellowship (FFF) Program is supported by specific foreign countries or areas. They provide opportunities for scientists to conduct collaborative research in the country that provides funding. The purpose of this program is to enhance the exchange of research experience and information in the biomedical, behavioral, and health sciences. The maximum period of support for all programs is 1 year, and the minimum period of support varies with each program. Participating countries are Finland, France, Federal Republic of Germany, Ireland, Israel, Japan, Norway, Sweden, Switzerland, and Taiwan, China.

PROGRAM HIGHLIGHTS

During FY 1989, only the IRF Program has international collaborations relating to nutritional research. Six ongoing foreign postdoctoral fellows are conducting nutrition research in U.S. laboratories. They are trophic and nutritional role of glutamine; nutrition and atherosclerosis risk; deteriorated frying oil, vitamin E and eicosanoid; study of amino acid metabolism in patients with burns; effects of glutamine supplementation; and dietary and genetic control of lipid transport.

For more information on the FIC programs in support of international research programs and fellowships, contact:

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NATIONAL CENTER FOR RESEARCH RESOURCES

The recently established NCRR represents the merger of two former divisions: the Division of Research Resources (DRR) and the Division of Research Services (DRS). DRR and DRS both conducted programs providing resources for the performance of biomedical research: DRR developed and supported research resources extramurally through grants, and DRS provided research services directly to NIH intramural scientists. The NCRR will continue to integrate and extend these activities, which play a significant role in NIH's scientific programs, including nutrition-related research. The NCRR has six extramural and four intramural components.

The six extramural components are the Animals Resources Program, the Biological Models and Materials Resources Program, the Biomedical Research Support Program, the Biomedical Research Technology Program, the General Clinical Research Centers Program, and the Research Centers in Minority Institutions Program.

The four intramural components are the Biomedical Engineering and Instrumentation Program, the Library Branch, the Medical Arts and Photography Branch, and the Veterinary Resources Program.

PROGRAM HIGHLIGHTS

Most of the extramural nutrition-related research is supported by the NCRR through its General Clinical Research Centers Program. The program funds a national network of 76 centers, usually organized as separate units within hospitals of academic medical centers. These centers provide clinical research resources for investigators supported by the categorical institutes of the NIH or by other peer-reviewed sources of funding. Resources include patient care facilities, with nursing and dietary support, and sophisticated laboratory technologies, including computer hardware and software. In addition, these centers introduce house staff and medical students to the interaction of basic and clinical research and

the translation of research results into clinical practice.

Other extramural program components of the NCRR also support resources for nutrition-related research.

All of NCRR's intramural nutrition-related research is through its Veterinary Resources Program.

A few highlights of extramural activities supported by NCRR in the area of nutrition follow.

Caloric Restriction and Aging

A prospective study of the consequences of caloric restriction on the processes of aging was initiated in 1989. The hypothesis being tested is that mild to moderate restriction of food intake will not only reduce the incidence and delay the onset of age-related diseases, but it also will slow the rate of aging and prolong the life span of primates as has been shown for rodents and some other species. Thirty 8- to 14-year-old male rhesus monkeys are being assessed semiannually in terms of insulin secretion and blood glucose regulation, immunologic function (lymphocyte responses to mitogens, natural killer cell activity), visual accommodation, body composition, sympathoadrenal activity, and metabolic rate. After collection of baseline data, half of the animals underwent gradual food restriction such that they now eat 30 percent less than their individual baseline amounts.

Whole Room Indirect Calorimeter

Support has been provided for a respiratory chamber-indirect calorimeter. The availability of this instrument will fill an important gap in present capabilities by allowing extended (24 hour) measurement intervals and precise calculation of energy-elemental balance with associated body composition changes. In addition, the availability of this instrument will allow

human studies of the relation of malnutrition to altered thermogenesis and thermoregulation. This indirect calorimetry system, one of a few in the nation, will be available to several researchers at five medical schools in the New York City area.

Dietary Intervention in the Treatment of Adrenomyeloneuropathy (AMN)

A randomized, prospective study has been undertaken, evaluating the biochemical and clinical efficacy of dietary intervention in men who are hemizygous for AMN and women who are heterozygous for AMN and who have neurological disability attributable to this condition. The dietary intervention consisted of supplemental feeding with GTO (glyceryl trioleate). Thirty-two men and 17 women were enrolled, by far the largest series of patients with this condition who have been systematically studied. A significant finding is that dietary GTO intervention is successful in achieving a 50 percent correction of the major biochemical defect, the abnormal accumulation of saturated very long chain fatty acids in plasma. Investigators are thus in a position to answer the central question, whether near normalization of this biochemical abnormality does or does not have a favorable effect on clinical outcome.

Potentiation of the Efficacy of L-dopa in Parkinson's Disease

It has been demonstrated that meals or snacks composed of carbohydrates (with or without fats) but lacking significant quantities of protein can exacerbate the clinical toxicity of L-dopa (e.g., the dyskinesias) in a parkinsonian patient, and that the effect of the carbohydrate is related to its ability to cause an insulin-mediated decline in plasma levels of the large, neutral amino acids (LNAA). This finding was anticipated based on earlier studies in rats. It complements the observation made two decades ago by Cotzias that dietary proteins diminish the efficacy of L-dopa by raising plasma levels of the competing amino

acids and thereby diminishing the transport of L-dopa across the blood-brain barrier.

The solution seems to be to give the patient nutritionally-balanced meals or snacks, i.e., those containing a ratio of protein to carbohydrates which will cause plasma LNAA levels neither to rise nor to fall. In a preliminary study, this nutritional strategy was found to work. A larger-scale study is now in progress.

RESEARCH DIRECTIONS

The following are examples of NCRR's nutrition-related extramural research support:

- Development of new x-ray microbeam techniques for measurement of trace elements *in situ* to allow researchers to relate amounts of elements such as chromium, cadmium and lead in teeth and bone to dietary and environmental exposures to these elements.
- Studies of malnutrition, cardiac dysfunction and gastrointestinal dysfunction in AIDS.
- Investigations of a new dietary therapy for adrenoleukodystrophy.
- Research on the relationships between obesity, body fat localization and non-insulin dependent diabetes.
- Studies on the rate and extent of absorption of L-carnitine (a conditionally essential nutrient for some human populations).
- Studies of protein catabolism in severely burned patients and in those who are septic (stress states).
- Research on affective and appetitive symptoms associated with the premenstrual syndrome.
- Studies of dietary iron availability in premature infants.

The following are examples of recent collaborations of NCRR intramural scientists with other NIH scientists and outside institutions in animal nutrition research:

- Investigations by the NIA to determine the influence of a calorie-restricted diet on the longevity of nonhuman primates.
- Long-term toxicology research by the NIEHS that requires a specially developed

diet for the long-term maintenance of rodents.

- Research by NASA to develop rodent diets that can be used effectively in a zero-gravity environment.
- Studies on the influence of various dietary constituents on hypertension in the spontaneously hypertensive rat.

OUTLOOK

The NCRR will continue to support resources essential to the conduct of biomedical research, which will lead to improved human health.

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Section 3. Highlights of Biomedical Research Programs in Nutrition



HIGHLIGHTS OF BIOMEDICAL RESEARCH PROGRAMS IN NUTRITION

The NIH nutrition research program includes extramural and intramural research and research training, and research manpower development. The major component of the program is the extramural research program carried out at various universities, in graduate science departments, principally in departments of nutrition; and medical, dental, and other health professional schools, especially schools of public health. A large portion of the research projects is based on ideas developed and submitted by individual investigators from research institutions throughout the nation and the world. Most of the intramural program is carried out on the NIH campus in Bethesda, Maryland, in laboratories and at the Clinical Center. The intramural program of the NIA is carried out at the Gerontology Research Center in Baltimore, Maryland; the NCI established a Laboratory for Nutrition and Cancer Research in Frederick, Maryland; some intramural nutrition research is conducted by the NIDDK at the Phoenix Epidemiology and Clinical Research Branch in Phoenix, Arizona; and the NIEHS is located in Research Triangle Park, North Carolina.

Three major funding mechanisms serve as administrative instruments for accomplishing NIH program goals through the efforts of scientists outside the NIH. These extramural mechanisms are financial assistance awards (grants and cooperative agreements) and acquisition awards (contracts), as described in appendix K. Awards are made to extramural institutions following a carefully executed scientific review known as the peer review process. Studies within the NIH intramural research program are also subject to scientific review.

The intramural and extramural research highlighted in this section does not provide a comprehensive list of the more than 2,400 nutrition research and training projects funded by the NIH in FY 1989, nor is it inclusive for each topic presented. Rather, for this issue of the annual report, we have chosen to present highlights of nutrition research on certain

selected topics and highlights of nutrition research conducted under center grants and program project grants, as well as highlights of international nutrition research activities and national nutrition monitoring research, to emphasize the diversity of the field.

HIGHLIGHTS OF NUTRITION RESEARCH: SELECTED TOPICS

The topical areas of nutrition research selected for inclusion in this report transcend institute boundaries. They illustrate activities related to the role of nutrition in preventing some of the most common diseases afflicting our population and to the role of nutrition in ameliorating rare diseases and conditions.

Nutrition and Disease Prevention in Minority Populations

In recent years, recognition of the role of nutrition in the maintenance of health and the prevention of disease has become widespread. The DNRC, the ICD representatives to the NCC, and the NES were extensively involved in the preparation and review of a major portion of the chapters in *The Surgeon General's Report on Nutrition and Health* (DHHS [PHS] Publication No. 88-50210, 1988). That report, published in 1988, reviewed the available scientific evidence and noted the association of diet with a variety of disorders. Among these are 5 of the 10 leading causes of death for Americans—coronary heart disease, stroke, atherosclerosis, diabetes, and some forms of cancer. Together, these illnesses account for two-thirds of all deaths in the United States and exact a substantial cost in terms of both direct health care and lost productivity due to treatment, disability, or premature mortality.

The report concluded that overconsumption of certain dietary components, rather than nutrient deficiency, is now a major concern in this country. For most Americans, the most likely nutrition problem is overeating—too

many calories for activity levels and an imbalance in the nutrients consumed. The report noted particularly the disproportionate consumption of foods high in fats, often at the expense of foods high in complex carbohydrates and fiber that may be more conducive to health. The nutrition-related diseases that rank among the leading causes of illness and death in the United States are diseases of dietary excess and imbalance.

High intake of total dietary fat is associated with increased risk for obesity and some types of cancer. Among the consequences of obesity are increased risk for diabetes mellitus, high blood pressure and stroke, coronary heart disease, some types of cancer, gallbladder diseases, and osteoarthritis of weight-bearing joints. Excessive saturated fat consumption is the major dietary contributor to high blood cholesterol levels, a risk factor for coronary heart disease.

Research on the role of nutrition in disease prevention has been highlighted in recent reports on the NIH program in nutrition research. In the *11th Annual Report of the National Institutes of Health Program in Biomedical and Behavioral Nutrition Research and Training* (NIH Publication No. 88-2092, 1988), the section on nutrition and disease prevention focused on heart disease, cancer, and obesity. In the *12th Annual Report of the National Institutes of Health Program in Biomedical and Behavioral Nutrition Research and Training* (NIH Publication No. 89-2092, 1989), this section dealt with stroke, diabetes, and osteoporosis.

The increasing appreciation for the role of nutrition in the prevention of these disorders has been accompanied by an increased recognition that the prevalence of various nutrition-related disorders and associated risk factors differs in different subgroups in the population. In fact, a disproportionate burden of diet-related disease is borne by subgroups in our population. Black Americans, for example, have higher rates of high blood pressure, strokes, diabetes, and other diseases associated with obesity (but lower rates of osteoporosis)

than the general population. Some groups of Native Americans exhibit the highest rates of diabetes in the world.

In this year's report, research on nutrition and disease prevention in minority populations with respect to obesity, cardiovascular disease, diabetes, and osteoporosis is highlighted.

The causes of these diseases are multifactorial, including genetic and environmental factors as well as diet and nutrition. The biomedical research approaches to understanding and preventing such disorders also are multifaceted. Epidemiological studies may be used to identify incidence, prevalence, risk factors, and groups at risk. Basic research protocols may be designed to discover mechanisms and possible metabolic pathways. Cellular and molecular research tries to determine biophysical alterations and contributes to the determination of ways to interrupt, reverse, or slow disease processes. Promising interventions, in the form of new drugs, practices, or procedures, may be tested in animal models for safety and efficacy and then in human subjects. If these prove successful, introduction into medical practice should follow. Education and demonstration projects can be used to provide information to the public and the effectiveness of preventive techniques can be evaluated. The nutrition-related research sponsored by the NIH on obesity, cardiovascular disease, diabetes, and osteoporosis encompasses many of these research approaches.

Obesity is very prevalent in the United States, affecting approximately 34 million adults ages 20-74 years. Obesity (or severe overweight) increases the risk for high blood cholesterol, high blood pressure, and diabetes, and, hence, for diseases for which these conditions are risk factors. It also increases the risk for gallbladder disease, for osteoarthritis of weight-bearing joints, and for some types of cancer and has significant psychosocial consequences. The high prevalence of obesity and its physical and mental health consequences motivate the high public health priority placed on its prevention.

The prevalence of obesity is disproportionately high in some subgroups of the population. National survey data indicate that the highest rates are observed in low-income and minority groups, especially low-income women and black and Mexican-American women. Prevalence rates are also strikingly high in some Native American population groups.

The term cardiovascular disease includes a variety of pathological processes pertaining to the heart and blood vessels, including coronary heart disease, atherosclerosis, hypertension, hypertensive heart disease, and cerebrovascular disease. Coronary heart disease still accounts for the largest number of deaths in the United States. More than 1.25 million heart attacks occur each year (two-thirds of them in men), and more than 500,000 persons die as a result.

Approximately 11 million Americans have diabetes, but almost half of them have not been diagnosed. In addition to the nearly 38,000 deaths in 1987 attributable directly to this condition, diabetes also contributes to an estimated 95,000 deaths per year from associated cardiovascular and kidney complications.

There are a variety of interrelationships between cardiovascular disease and diabetes. Obesity is a risk factor for coronary heart disease, hypertension, stroke, and diabetes. Diabetes itself promotes hypertension and is a predisposing factor for stroke.

Coronary heart disease mortality is substantially higher in males than in females. Hypertension and stroke are more prevalent in black than white Americans. The prevalence of diabetes is significantly higher in Hispanics and some American Indian groups than in the general population.

Approximately 15 to 20 million Americans are affected by osteoporosis, which contributes to some 1.3 million bone fractures per year in persons 45 years and older. One-third of women aged 65 years and older have vertebral fractures. On the basis of x-ray evidence, by

age 90, one-third of women and one-sixth of men will have suffered hip fractures, leading to death in 12 to 20 percent of those cases and to long-term nursing care for many who survive.

The incidence of osteoporosis and the risk of fracture is significantly higher for women than for men. Blacks in the United States experience fewer osteoporotic fractures and have a higher bone density and higher bone mass than do whites. Asian Americans have less cortical bone mass than do whites. However, relatively little is known about the incidence of osteoporosis and the fracture rate in Asians or other minority populations, such as various Hispanic groups.

The following accounts describe NIH-supported research highlights related to nutrition and the prevention of obesity, cardiovascular disease, diabetes, and osteoporosis in minority populations (see also the individual institute reports in section 2):

- Obesity is regarded as a significant predictor of coronary heart disease (CHD) and is also one of the major public health problems in black women. It is positively associated with elevated blood pressure, blood triglycerides and very low density lipoproteins, and diabetes, and negatively associated with high density lipoproteins. Obesity in black women, often developing in adolescence, has been suggested as a major contributor to higher coronary heart disease mortality among black compared with white adult women.

During 5 years of field study, a multicenter program will investigate the occurrence of obesity in black and white children, the predictors of transition to the obese state, the correlates of this transition, and the relationship of this transition to other CHD risk factors. Three clinical sites and a coordinating center were selected for this program in 1985. Two projects obtained subjects through community schools, the third through members of a group health program. A study protocol was developed to recruit, examine, and follow longitudinally

black and white female children, 9 and 10 years of age at entry. Parents or guardians of the children are included in the study and its examinations. Data gathering forms were cleared by the OMB in December 1986. Pilot studies were completed in early 1987, and recruitment began in March and April 1987. Currently, the second follow-up year examinations are nearing completion.

The first examinations and interviews were concluded in February 1988. Enrollment was completed for 2,328 girls, 48 percent white and 52 percent black, and 2,236 parents or guardians. The second exam year indicated a reexam rate of approximately 95 percent, and the third year, currently under way, about 90 percent. Data entry, as well as analysis of data from examinations, nutritional forms, laboratory tests and questionnaires, is ongoing. The results should aid in providing a basis for effective therapeutic intervention programs for prevention of obesity.

- Another study has been designed to clarify the causes of the increased prevalence of obesity in black women. It includes investigation of whether there is a defect in thermogenesis in black women relative to white women. The study also is planned to determine whether differences exist in fat cell morphology and/or fat cell metabolism between black and white women which may produce a differing metabolic milieu predisposing to the development of the complications of obesity in black women. The resting metabolic rate, the thermic effect of food after a standard meal, and the nutrients oxidized and stored will be measured in black and white women of similar obesity and age. Metabolic and other tests will be performed to characterize upper and lower body obesity to determine whether the location of fat correlates to health risks and whether the risks differ in black and white women. Studies also are ongoing to examine the sociological and physiological mechanisms leading to weight gain and the efficacy of weight reduction therapy in black women.

- The Pima Indian population of the Gila River Indian Community in Arizona has the highest reported frequency of noninsulin-dependent diabetes in the world as well as a very high prevalence of obesity, gallbladder disease, and several types of arthritis, including rheumatoid arthritis and ankylosing spondylitis. The nature of the Pima Indian community and the fact that long-term epidemiological and clinical research studies have been performed within it for many years have resulted in a data base in which it is possible to conduct comprehensive investigations of the occurrence and determinants of these diseases and their complications.

Investigations of the determinants and pathogenesis of obesity in this population have focused on a number of different aspects of energy metabolism. Previous work demonstrated that individuals with lower metabolic rates were at greatest risk of subsequent weight gain over several years. Further investigations have demonstrated that differences in respiratory quotient represent an additional risk factor for weight gain and provided evidence that the preferential utilization of carbohydrate or conversely a low rate of lipid oxidation, reflected in a change in respiratory quotient, represents an additional risk factor for the development of obesity.

Until recently it has been difficult to assess the role of physical activity in energy metabolism and the pathogenesis of obesity. Now using a doubly labeled water technique, it is possible to measure energy expenditure under free-living conditions. This method has been implemented and carefully validated against the accurate energy expenditure measurements obtained from the respiratory chamber. The doubly labeled water technique has been shown to be an accurate alternative method of measuring energy metabolism. New studies have been planned to use this technique to determine the effect of physical activity on energy metabolism in the free-living state.

- Recent data indicate that cardiovascular disease (CVD) has become the leading cause of death in American Indians. While some Indian groups appear to be participating in the decline in CVD within the general U.S. population, among others, rates appear to be increasing. A multicenter research program has been initiated to determine the rates of CVD among American Indians and to measure the levels of CVD risk factors among American Indians in three different geographic areas of the United States. Protocol development, pilot testing and training, and over 1,100 of 4,500 projected examinations have been completed. Preliminary analyses of limited data indicate significant differences among centers for CVD risk factors.

- Coronary Artery (Disease) Risk Development in (Young) Adults (CARDIA) is a study of the distribution and evolution of risk factors for CVD in a sample of 18- to 30-year-old black and white males and females with a range of attained education. CARDIA is designed to increase understanding of contributors to changes in CVD risk factors during the critical years of transition from adolescence through young adulthood to middle age.

CARDIA was funded initially in 1983 for a 5-year cycle that included two rounds of examinations. Four clinical centers (Birmingham, AL, Chicago, IL, Minneapolis, MN and Oakland, CA) and a Data Coordinating Center (Birmingham, AL) were selected. The initial examination series was successful with 5,164 subjects recruited. Adequate numbers from the desired age, sex, race, educational groups were recruited so that the planned comparisons among subgroups could be made. A second CARDIA examination has been completed. Over 90 percent of the original cohort was reexamined.

The primary objectives of CARDIA are to document at baseline and at approximately 2-year intervals, levels of risk factors for coronary artery disease and potential

determinants of these risk factors in subjects 18 to 30 years old at the time of entry into the study; to examine the interrelationships of risk factors and lifestyles; to document behavioral and environmental changes during the transition from adolescence to middle age; and to compare cross-sectional and longitudinal data on age related trends in CVD risk factors. The secondary objectives of CARDIA are to compare levels and evolution of risk factors between males and females, blacks and whites, and in groups of differing geographic and socioeconomic status.

The basic approach during the second 5 years of the CARDIA study will be the same as that utilized during the initial study period. Measures of established CVD risk factors, lifestyles, nutritional habits, and stressful life events will be included. Examinations on individual subjects will continue to be performed at 2-year intervals. Since the major changes to be anticipated within this age group are in blood pressure and degree of obesity, special emphasis will be placed on the evaluation of these CVD risk factors.

- The Atherosclerosis Risk in Communities (ARIC) is a large-scale, long-term program that will measure associations of established and suspected CHD risk factors with both atherosclerosis and new CHD events in men and women from four diverse communities. The project has two components: community surveillance and repeated examinations of a representative cohort of men and women in each community. The community surveillance involves abstracting hospital records and death certificates and investigating out-of-hospital deaths. The representative cohorts include 4,000 persons from each community. Three of these reflect the ethnic composition of the communities in which they live; one cohort is black. All cohort participants will be examined twice during the initial 8-year contract period (1985-1993) and contacted annually to update their medical histories.

Atherosclerosis is measured by carotid and popliteal ultrasonography. Risk factors studied include blood levels of lipids, lipoprotein cholesterol, and apolipoproteins; plasma hemostatic factors; blood chemistries and hematology; sitting, supine and standing blood pressures; anthropometry; fasting blood glucose and insulin levels; ECG findings; cigarette and alcohol use; physical activity levels; dietary aspects; and family history.

The diverse communities can be compared with respect to CHD incidence and medical care and, through the cohort component, with respect to risk factors and peripheral atherosclerosis. The results will provide a measure of the variation in the distribution and determinants of CHD in the United States and, within the limits of ecologic analysis, suggest possible reasons for observed differences. The information will allow comparison with the other countries in the WHO MONICA project.

- Prior studies of black-white differences in hypertension and coronary disease have compared racial groups from markedly different socioeconomic and educational backgrounds. A new study is being conducted to examine the natural histories of coronary artery disease and hypertension in cohorts of 435 black and 573 white men with identical occupation and education (physicians who are alumni of two medical schools). First, the prevalence and incidence of coronary artery disease, hypertension, and other cardiovascular diseases will be compared using standardized end point criteria. Second, the prevalence of cardiovascular risk factors such as smoking, diabetes, family history, dietary factors, and lipoprotein cholesterol levels will be compared between cohorts in midlife. Third, the youthful predictors of midlife cardiovascular risk factors will be determined using baseline data collected by identical protocols in the two cohort between 1957 and 1965. Finally, the

youthful risk factors will be related to the incidence of disease in midlife in the two cohorts to identify differences in significance, independence, and relative importance of risk factors in blacks vs. whites. Knowledge to be obtained from this study regarding black-white differences in the course and causes of hypertension and coronary artery disease is needed to develop both effective treatment and prevention strategies for both black and white Americans.

- A long-term (25-year) prospective study of more than 2,000 subjects from a single community is being conducted to examine the relationship of obesity and fat patterning with morbidity and mortality in black Americans. Recent studies have shown that fat patterning is an important risk factor for diabetes and possibly cardiovascular disease. Diabetes and cardiovascular disease are among the six causes of death that contribute most to the disparity in death rates between blacks and whites, yet the relationship of fat patterning with these diseases is largely unstudied in blacks. Because there are known racial differences in growth rates, body proportions, and adiposity, it cannot be assumed that studies performed on whites are applicable to blacks. This research will provide important information concerning the role of adiposity and fat patterning in diabetes and cardiovascular disease in blacks and has implications for the prevention and treatment of these diseases.
- An epidemiologic survey of cardiovascular risk factors and diabetes in Mexican Americans and non-Hispanic whites living in San Antonio recently has been completed. Results indicate that Mexican Americans have excess diabetes and related cardiovascular risk factors over and above that which can be explained on the basis of their excess obesity alone. A further epidemiologic survey is planned to elucidate the role of additional factors beyond obesity, such as lifestyle and genetic

differences, that contribute to diabetes and cardiovascular risk in this ethnic group. The prevalence of diabetic complications in Mexican Americans and non-Hispanic whites with diabetes in the two surveys also will be determined.

- Another study has been designed to assess the degree to which several factors including diet are related to obesity in Mexican-American and non-Hispanic white preschool children. A sample of 180 Mexican-American children, 3-5 years of age, and their mothers, and a sample of 1,890 non-Hispanic white children, 3-5 years of age, and their mothers will participate in the study. The findings are intended to provide a research base for the development of intervention studies.
- Researchers are conducting investigations designed to determine if genetic, immunological, and clinical variables can be utilized to distinguish between black women with gestational diabetes mellitus who will subsequently become noninsulin-dependent diabetic and those who will remain normal. Over 400 patients are being followed longitudinally to determine if parity, obesity, body fat distribution, fetal outcome, hypertension, thyroid disorders, family history of diabetes and/or heart disease, and various genetic markers are risk factors for these women developing overt diabetes. The relationship of lifestyle, socioeconomic status, dietary habits, and personality traits, as assessed by a health hazard appraisal type of instrument, to the subsequent development of overt diabetes also is being assessed. Measures, such as serum lipid levels, that will aid in examining the etiological relationships between diabetes and other diseases are collected at yearly follow-up visits. Results of this study should provide a clearer understanding of risk factors for the subsequent development of noninsulin dependent diabetes, insulin dependent diabetes, and other diseases that often coexist with diabetes in black women.
- Recent in-depth analysis of data gathered during the Second U.S. National Health and Nutrition Examination Survey has uncovered interesting new information on the relationship of obesity to the increased prevalence of diabetes in African Americans. The results suggest that this racial group has no greater burden of diabetes at normal body weight. However, as their weight progressively exceeds the normal range, African Americans appear to develop diabetes at a disproportionately high frequency when compared to whites. If confirmed, this has implications for the potential public health role of effective weight maintenance in this minority population.
- Knowledge of racial differences in body composition and bone density is useful for the understanding of both obesity and osteoporosis. In a recent study, comparisons were made on body composition and bone density among Asians, blacks, and whites, age adjusted. In males, Asians are 2 percent fatter ($23 \pm 6\%$) than blacks ($21 \pm 7\%$) and whites ($20 \pm 7\%$). Total body bone densities decrease in the order of blacks > whites > Asians (1.28 ± 0.11 , 1.18 ± 0.12 , and 1.14 ± 0.09 mg/cm², respectively). The results in females are different from those in males. Fat content in Asians ($34 \pm 7\%$) and blacks ($35 \pm 10\%$) is similar and higher than in whites ($31 \pm 9\%$). Bone densities in Asians (1.02 ± 0.9) and whites (1.06 ± 0.11) are similar, but both are lower than in blacks (1.18 ± 0.13). The water content in LBM in whites is 0.74 ± 0.06 , similar to that reported in the literature. However, Asians have a surprisingly high water/LBM ratio of 0.78 ± 0.08 . Blacks are between Asians and whites but not different from either ethnic group. The TBK/LBM ratio and the density of LBM are similar in all female groups. The anthropometric measurements show that female blacks, like male blacks, have both longer thighs and greater upper body fat than Asians and whites. These data show that body composition varies with sex and ethnicity. The previously assumed

"biological constancy" of the density, the water content, and the potassium content of the lean body have been shown to be incorrect, with the degree of error increasing with age and fatness in each ethnic group.

- Mexican Americans have an incidence of hip fracture about one-half that of non-Hispanic whites. The reasons for this lower risk are unclear, but lower fracture risk in other ethnic groups, e.g., blacks, have been ascribed to greater bone mass. The bone mass of Mexican Americans and the relationship of bone mass to risk factors has never been examined. A new study has been designed to determine the bone mass of the hip and spine, sites of the most clinically important osteoporotic fractures, in a population based sample of 400 Mexican American and non-Hispanic white women who have been followed since 1979. Several risk factors for osteoporosis, such as obesity, diet, exercise, and medication use, have been studied prospectively in this population. Additional risk factors for osteoporosis will be assessed by questionnaire, and bone mass will be measured by dual photon absorptiometry. These data will be used to identify any differences in bone mass between Mexican Americans and non-Hispanic whites and to assess which risk factors might account for these differences. These data also will be used to develop predictive models relating risk factors to the bone mass of individuals. The results of this study may yield useful guidance to clinicians and health care planners by indicating if and for whom bone mass measurements add any substantial information about fracture risk above that provided by clinical assessment alone.

Nutrition and Rare Diseases and Conditions

Nutrition also plays a critically important role in a variety of rare diseases and conditions. In recent years there has been substantial interest in the development of therapies for rare disorders, many of which have been shown to

be amenable to nutritional intervention. A rare disease or condition was defined in the Orphan Drug Act (P.L. 97-414 as amended), in terms of a prevalence criterion, as one that affects fewer than 200,000 persons in the United States.

One large class of rare diseases is represented by a subgroup of genetic disorders, the inborn errors of metabolism. In these disorders, the genetic defect is expressed by the production of an enzyme deficient in its capacity to catalyze and modulate the enzymic function of concerting substrate to product. Despite their relative rarity, the classical inborn errors have had a clinical and research importance far out of proportion to their number. The diseases that result from inborn errors are based in every organ system, which gives them a significance for all medical specialties and subspecialties. Inborn errors have played significant roles in the elucidation of normal physiological pathways and the pathogenesis of disorders within them. Many inborn errors have been identified; much current research focuses on describing variants of known disorders.

Nutritional therapies have been developed for many of the inborn errors of metabolism; in some cases, studies that led to their development have provided insights into normal nutritional requirements as well. Although many nutritional therapies for such disorders are protective of cognitive function, they often do not effectively eliminate all disease complications, and they sometimes produce secondary nutritional deficiencies. Current research is designed to improve existing nutritional therapies, as well as to develop new ones.

The following are highlights of NIH-supported research on the role of nutrition in rare diseases and conditions, including inborn errors of metabolism:

- Women with phenylketonuria (PKU) diagnosed and treated at birth are intellectually normal, but are at risk for maternal PKU syndrome in their offspring (mental retardation, microencephaly, heart

defects, and low birth weight) if blood phenylalanine levels are not controlled by diet throughout pregnancy. Researchers are working to ascertain the most beneficial low-phenylalanine diet, in terms of both concentration of phenylalanine and timing of the diet, for the prevention of maternal PKU. Tyrosine and trace element status are also of concern (see also section 2).

- Gyrate atrophy of the chorioretina that is due to ornithine ketoacid transaminase deficiency, with consequent hyperornithinemia, is an autosomal recessive disorder. Genetic heterogeneity of gyrate atrophy has been suggested by the observation that administration of pyridoxine to increase the level of pyridoxal phosphate available as an enzyme cofactor reduces the hyperornithinemia in a subset of patients. Researchers have recently found that the pyridoxine-responsive and pyridoxine-nonresponsive variants may be distinguished by the *in vitro* responsiveness to pyridoxal phosphate of fibroblasts obtained from patients with the two variants.
- Biotinidase is the enzyme that cleaves biotin from the final products of the proteolytic degradation of biotin-dependent carboxylases, thereby recycling the vitamin. Biotinidase activity is deficient in most children with late-onset multiple carboxylase deficiency. Affected children may exhibit symptoms including seizures, hypotonia, ataxia, skin rash, and developmental delay, which may progress to coma and ultimately to death. All children with biotinidase deficiency who have been treated with biotin have improved clinically. Investigators have been collaborating on newborn screening programs for biotinidase deficiency to obtain a better understanding of the initial features and natural history of the disorder.
- A recent case report illustrates how the presence of a distorted sense of smell led to the diagnosis of the rare metabolic disorder trimethylaminuria. The patient received

dietary counseling to avoid choline-containing foods, and these modifications alleviated the patient's symptoms.

- Adrenoleukodystrophy (ALD) and adrenomyeloneuropathy (AMN), are related genetic metabolic diseases that follow an X-linked pattern of inheritance. ALD manifests itself early in life, with a mean onset at approximately age 7, by the appearance of symptoms such as endocrine deficits, cerebral demyelination, and testicular changes, all of which lead to gradual severe neurologic disability and death. AMN is a late onset disease that involves adults and manifests itself through a slowly progressive spinal cord and peripheral nerve involvement leading to disabilities and morbidity. Some female carriers develop late onset symptoms of variable magnitude and gravity.

A peroxisomal enzyme defect results in an impaired ability to oxidize very long-chain saturated fatty acids (VLCFA) in ALD. The accumulation of these VLCFA in the central nervous system (CNS) appears to cause the devastating demyelination of the CNS in the fatal childhood and adolescent forms of ALD and the demyelination of the peripheral nervous system in the milder late onset form of AMN. In both disease forms there are also various degrees of adrenal insufficiency. Preliminary experiments indicated that the synthesis of the major VLCFA was decreased in cultured fibroblasts from ALD patients when the cells were grown in the presence of monounsaturated fatty acids resulting in decrease in cellular VLCFA accumulation. Preliminary clinical trials, performed independently by researchers in two laboratories, showed that dietary administration of oleic acid (as glycerol trioleate) and erucic acid (as glycerol trierucate) lowered the circulating levels of VLCFA. Oleic acid was found effective but erucic acid was even more effective. In a double-blind crossover study of ALD patients on chronic oleic acid therapy, the addition of erucic acid to the diet led to a

further VLCFA reduction in the treated patients' plasma. Promising therapeutic results led to the initiation of a large scale therapeutic clinical trial in ALD and AMN patients (see also section 2).

- A major respiratory complication of respiratory distress syndrome (RDS) in premature infants is bronchopulmonary dysplasia (BPD), a chronic lung disorder that was first recognized in 1967. The condition involves abnormalities in the architecture of the lung that lead to poor gas exchange and, in many instances, progressive respiratory failure. Approximately 1,300 infants survive each year with BPD in the United States. Much research is now being done on BPD, but many questions remain to be answered.

Some recent work approached the problem of BPD from the assumption that its pathogenesis originates, not from injury to the lung, but during the lung repair process. It has been known for some time that vitamin A augments epithelial cell repair following injury and that very low birthweight neonates are often deficient in vitamin A. A recent clinical study has demonstrated that vitamin A supplementation in premature infants who are dependent on mechanical ventilation and oxygen promotes lung healing and reduces the incidence and severity of BPD. The efficacy and safety of treating premature neonates with vitamin A has yet to be established. This study is a first step in the evaluation of vitamin A supplementation as a means of reducing the incidence of chronic lung disease in premature infants.

HIGHLIGHTS OF NUTRITION RESEARCH: CENTER GRANTS AND PROGRAM PROJECTS

Clinical Nutrition Research Units

As a means of encouraging a multidisciplinary approach to clinical nutrition research, the NIH has sought to foster the development and

operation of Clinical Nutrition Research Units (CNRUs) through the establishment of a CNRU program in 1979. Two NIH institutes, the NIDDK and NCI, support these units. Specific objectives of a CNRU are as follows:

- To create or strengthen a focus in a biomedical research institution for multidisciplinary research in clinical nutrition, in order to develop new knowledge about specific nutrients in health throughout the human life cycle, and in the prevention and treatment of disease.
- To strengthen training environments in order to improve the education of medical students, house staff, practicing physicians, and allied health personnel in clinical nutrition.
- To enhance patient care and promote good health by focusing attention on clinical nutrition and generating nutritional information for the public.

The essential components of a CNRU include the following elements:

- Research with human subjects and populations;
- Laboratory investigations;
- Research training (funds derived from other sources);
- Shared facilities and research resources;
- Education programs for medical students, house staff, practicing physicians, and allied health professionals (funds derived from other sources);
- Research components of nutritional support services;
- Public information activities (funds derived from other sources).

To qualify for the award of a CNRU grant, the potential applicant institution or consortium of institutions must already have a substantial base of ongoing, independently supported, peer-reviewed research in the nutritional sciences. This initial required research base is formed from a group of investigators with individually funded research projects who can benefit from

shared resources. Thus, the CNRU grant is intended to provide an added dimension that includes the capability and the potential for accomplishments greater than that possible by the support of individual projects alone.

A CNRU must be an identifiable organizational unit within a single university medical center or a consortium of cooperating institutions. The overall goal of a CNRU is to bring together, on a cooperative basis, basic science and clinical investigators in a manner that will enrich the effectiveness of research in nutritional sciences. A program of excellence in biomedical research in this area must be in existence at the time of submission of a CNRU application. Close cooperation, communication, and collaboration among all center personnel of many professional disciplines are characteristics of a successful CNRU. A successful CNRU also will attract into the CNRU talented scientists from disciplines other than nutrition.

The major source for support of biomedical research projects associated with the CNRU is derived from the separately funded projects of the participating investigators. Similarly, stipends for professional trainees in research are not available through CNRU funding; rather, such funding must be sought through other mechanisms.

Core facilities of CNRUs are developed to support research in the broad areas of fundamental and clinical nutrition. Application of state-of-the-art techniques in the areas of cell biology, molecular biology, immunology, and integrative physiology is encouraged to increase knowledge concerning the function and requirements of nutrients, the relationship of diet (and nutrients) to health and disease, and the prevention and treatment of disease as an outgrowth of nutrition research.

Core facilities in a CNRU are shared resources that enhance productivity or in other ways benefit a group of investigators working to accomplish the stated goals of the CNRU. Two other types of activities also may be supported

with CNRU funding—a pilot and feasibility program and an enrichment program. The pilot and feasibility program provides modest support for new initiatives or feasibility studies for new investigators who are in research areas of direct interest to the CNRU. These areas may include biomedical, epidemiologic, or behavioral research as they pertain to the CNRU goals. The enrichment program provides limited funds to sponsor seminars, visiting scientists, workshops, etc.

Brief descriptions of the activities of CNRU facilities functioning in FY 1989 are given below:

- The CNRU at the University of California, Davis (supported by NIDDK) promotes interdisciplinary research among nutrition scientists in the Schools of Medicine and Veterinary Medicine and in the College of Agriculture. Five general research themes are encompassed: nutrition and development; nutrition and intestinal function; nutrition and immunity; regulation of food intake and the pathogenesis of obesity; and nutritional support of acute and chronically ill patients. Research in these areas is supported by centralized Core Laboratories which provide assays of vitamins and minerals, metabolic substrates, and clinical biological samples, and which support methodologies in cell biology and in studies of food intake. Funds from the CNRU are applied directly to support a new investigator and six pilot and feasibility studies in clinical nutrition. An enrichment program has heightened the visibility of clinical nutrition research in the university, through support of regular scientific seminars and a visiting professor program.

Researchers at the CNRU have recently demonstrated:

- the association of intestinal malabsorption with mucosal HIV infection, suggesting a potential role for antiviral treatment directed at the mucosal lesion early in the course of the disease;

- the lack of effect of intravenous fat infusion on glucose oxidation in patients with sepsis;
 - the potential for taurine deficiency in premature infants receiving TPN because of the inability of the immature kidney to conserve the amino acid;
 - the dietary requirement for pyrroloquinoline quinone in mice; and
 - the characteristics of women who successfully maintained a weight loss of 20 pounds or more (they exercised more, smoked less, and appeared to have better problem solving skills than women who did not maintain weight loss).
- The principal aim of the CNRU at the University of Alabama in Birmingham (supported by NCI) is to continue various interdisciplinary research activities, development of clinical nutrition support procedures, and educational functions that have characterized progress over the past 6 years. Another major goal is the graduate program leading to a Ph.D. in human nutrition. The Core Nutrition Center will enhance the training environment and also will benefit from the efforts and intellectual stimulation of graduate students. Additional goals include carrying out a series of studies regarding nutrition and cancer, including studies on cancer chemoprevention, and extending the capabilities of the diagnostic laboratories by offering automated assays for an increased number of micronutrients, including vitamins, amino acids, and trace elements on small biological specimens.

Recent research conducted at the CNRU includes:

- a successful trial of folic acid to control methotrexate toxicity during low-dose therapy of rheumatoid arthritis;
 - promising trials of new antifolates for the treatment of autoimmune diseases;
 - studies of 4-hydroxy-phenyl-retinamide, a retinoid with a strong anti-promotional effect, which indicated that it may facilitate tumor initiation;
 - a study of canthaxanthin, a carotenoid without vitamin A activity, which indicated that this compound prevents cancer initiation but has no effect on cancer promotion; and
 - an examination of the folate content of desquamated oral mucosa cells which detected localized deficiencies of folate in the tissues of smokers while circulating levels of folate were within normal limits.
- The CNRU at Memorial Sloan-Kettering Cancer Center (supported by NCI) is becoming the central mechanism for the major nutrition efforts of the participating institutions, i.e., Memorial Sloan-Kettering Cancer Center, The New York Hospital-Cornell Medical Center, and The Rockefeller University. Core laboratories focus on biophysics, immunology, metabolism and metals, lipids, and metabolic bone disease. The CNRU Nutrition Information Center was established in the second year of this program. Its activities continue to involve development of a nutrition "Hotline" as well as initiation, collection, and dissemination of nutrition materials to the professional community first and later to the general public.

CNRU researchers have recently:

- detected a profound deficiency in the dietary intake of calcium in a cohort of healthy cancer survivors;
- shown that in patients with anorexia nervosa and bulimia nervosa there is a direct relationship between serum cortisol secretory rate and bone density;
- demonstrated in an animal carcinogenesis model that a "stress diet" that resembles the typical Western-style diet (high in fat and phosphate and low in calcium and vitamin D) induces hyperproliferation and hyperplasia in the colonic mucosa; and
- found that cancer patients who consumed a typical macrobiotic diet had prolonged antipyrine half-lives compared to patients on a typical Western diet, suggesting that reduced cytochrome P-450 activities may

render such patients more susceptible to the toxic effects of chemotherapeutic drugs.

- The University of Washington CNRU (supported by NIDDK) encompasses a wide ranging scope of nutrition-related research being conducted in a diversity of disciplines. Studies range from in-depth basic research, nutritional studies using laboratory animals, metabolic ward and outpatient clinical investigation, to epidemiological and intervention studies. The overall goal of these studies is to provide an in-depth, better understanding of the physiology of fuel utilization and clinical disorders that can be related to nutrition, both from a causal and therapeutic standpoint. Several major areas are under investigation, including nutritional aspects of atherosclerotic heart disease, diabetes, lipid metabolism, metabolic bone disease, obesity, nutrition in the elderly, and nutrition and cancer. The three cores of the CNRU are:
 - a Laboratory Core to provide affiliate investigators with cost-efficient, state-of-the-art nutritional assays and to help with new method development;
 - a Clinical Nutrition Research Core to provide facilities and help for investigators with their clinical research, and to provide a patients registry and biostatistical unit; and
 - an Administrative Core, which is responsible for the day-to-day administration of the CNRU.

Research conducted recently by investigators at the CNRU has indicated that:

- patients whose plasma lipid levels were aggressively lowered by diet and drugs had a net regression of coronary artery disease, compared to net progression in the controls, and a 75 percent reduction in clinical events;
- heterozygotes for lipoprotein lipase deficiency represent a distinct subset of familial combined hyperlipidemia;
- the use of omega-3 fatty acids in patients with noninsulin-dependent diabetes is likely to lead to worsening of glycemic control; and

- treatment with thiazide diuretics in nonhuman primates helps to prevent the mineral and bone loss that occurs in metabolic bone disease during parenteral nutrition.

- The CNRU at the University of Wisconsin (supported by NIDDK), with its staff and Core Laboratory, acted as the conduit to initiate collaborative efforts in research between the basic and clinical scientists across the campus. These accomplishments of the CNRU in terms of research can best be discussed in relation to cooperative arrangements with large multi-investigator programs as well as with recognized research programs of individual established investigators.
 - Clinical Cancer Center. In collaboration with the staff of a large protocol on the efficacy of interferon in cancer patients, the staff of the CNRU, using the facilities of the Core Laboratory, carried out an in-depth investigation in treated patients on the effect of interferon on total and HDL cholesterol levels. The effect was determined to be due to interferon itself in that the impure alpha leukocyte interferon, more purified preparations, and finally recombinant DNA alpha leukocyte interferon all produced the same effect.
 - Renal Dialysis Program. A collaborative study was organized with the Nephrology Section of the Department of Medicine that maintains a large dialysis treatment unit. This study demonstrated that carnitine was lost into the dialysis fluid in considerable amounts.
 - Preventive Cardiology and Biodynamics Laboratory. There has been a long history of research at the Biodynamic Laboratory on the effects of exercise conditioning in the relationship to the development of cardiovascular disease. The CNRU has entered into a collaborative effort with the program, and the Core Laboratory carries out all serum lipid analyses for research protocols.
 - Gastroenterology. This division of the Department of Medicine serves as a major source of support in terms of both research

and training in clinical nutrition. A definitive study found that a kidney bean alpha amylase inhibitor (starch blocker) was ineffective.

- The CNRU at the Harbor-UCLA Medical Center (supported by NCI) seeks to promote both clinical and fundamental research on the role of nutrition in cancer prevention and cancer treatment; encourage advancements in nutrition education at the UCLA hospitals and campus; and foster an interdisciplinary approach to problems in cancer nutrition. The CNRU is organized around four core laboratories:
 - The Vitamin/Trace Element Core offers a wide variety of assays of vitamins and trace elements associated with cancer. The laboratory has collaborative arrangements with investigators studying colonic polyps, anorexia nervosa, niacin assessment, dietary fatty acids, carotenoids, and methyl group deficiency.
 - The Lipid/Hormone Core is equipped to offer routine assays of a number of hormones which may play a role in the prevention or development of cancer and a number of fatty acids and derivatives which are useful in assessing the role dietary fats may play in the development of cancers. Collaborative efforts include studies of blood cell sensitivity to chemotherapy, lipid and steroid levels in patients with benign and malignant tumor tissue, hyperlipidemia and etretinate therapy, dietary fat and colonic cell proliferation, and oncogenes and dietary promotion of breast cancer.
 - The Mutagenesis Core offers bacterial assays for mutagenicity and has developed a method to quantify the levels of fecal mutagens. Collaborative efforts include studies on the risk to cancer nurses handling anticancer drugs, measurement of fecal mutagens in normal adults and in patients with gastrointestinal malfunction and in infants and newborns, and the antimutagenic properties of carageenans.
 - The Stable Isotope Core offers GC/MS quantification of certain stable isotope-labelled compounds. Studies under way include the development of techniques for

measuring the levels of glucose, lactate, and several amino acids; the rate of synthesis, turnover, and breakdown of these compounds might be expected to change in cancer, especially in states which lead to cachexia.

- At the University of Chicago, the core laboratories of the CNRU (supported by NIDDK) have participated in the following activities:
 - Stable Isotope Laboratory. Recent application to humans of the promising, non-invasive doubly labeled water approach to the assessment of energy expenditure in the free-living individual has attracted a large number of new collaborators from a variety of different departments here and at other institutions.
 - Vitamin Assay Laboratory. In addition to the assays for folate, 25-hydroxy vitamin D, and folate binding proteins, this laboratory has developed assays for thiamin, riboflavin, pyridoxine, and ascorbic acid. A new high pressure liquid chromatograph (HPLC) has been developed capable of measuring vitamin A and vitamin E by HPLC as well as vitamin A esters. The laboratory has developed methodology for the HPLC measurement of NAD, niacin, and other related metabolites, various forms of folate, and other B vitamins including coenzyme A and pantothenic acid.
 - Trace Element Laboratory. The laboratory has carried out a dual mission of the development of improved methods for the determination of trace elements in the clinical setting while offering analytical capabilities to investigators for standard trace element assays.
 - Radioimmunoassay Laboratory. The laboratory provides nutrition oriented investigators with important hormonal assays, including insulin, glucagon, and D-peptide. The laboratory developed techniques for the determination of somatostatin-like immunoreactivity.
 - Lipid Laboratories. There are two core laboratories in lipids. One has extended the capacity of the Lipid Core Laboratory of the SCOR Atherosclerosis NIH grant and provides potential nutrition investigators

with highly reliable assays of serum cholesterol, HDL cholesterol, triglycerides, and fatty acids. The other is capable of providing a detailed ultracentrifugal lipoprotein profile. In addition, the laboratory offers apolipoprotein analyses by radioimmunoassay.

- **Study Design and Data Management.** This facility provides resources for all CNRU investigators in consultation about statistical and other concerns relative to initial study design, assistance in randomization and conduct of blinded studies, and data analysis and interpretation. The other major function of this unit is to provide programming support for data analysis and interpretation.

- At Vanderbilt University, the CNRU (supported by NIDDK) comprises an Administrative Core, Analytical Laboratory Core, Nutrient Transport Core, Mass Spectrometry Core, and Energy Balance Core. Six clinical nutrition research projects serve as a focus for CNRU activity and include the following studies:
 - nutritional hepatic encephalopathy;
 - optimal intake of zinc and copper in pediatric patients requiring total parenteral nutrition or defined formula diets;
 - micronutrient metabolism in patients with essential fatty acid deficiency;
 - preliminary assessment of the efficacy of supplemental enteral tube feedings as an adjunct to combination chemotherapy in patients with small cell and anaplastic carcinoma of the lung;
 - effects of chronic dialysis and uremia on vitamin and trace element metabolism in children and adults; and
 - nutritional assessments as predictors for determining need for special nutritional support in presurgical patients.

Additionally, a pilot study to develop and utilize accurate, inexpensive, and timely screening tools for identifying undernourished hospital patients at admission is in progress. A brief nutrition questionnaire, the height-weight index, and computerized screening of potentially

nutrition-related routine laboratory data serve as the basis for screening of all admissions. The CNRU Metabolic Assessment Laboratory is developing age- and sex-related normal ranges for vitamin, mineral, and functional protein assays. Schemas have been devised for each project and the Clinfo computer system is in use for the storage and analysis of data.

Nutrition Research in the General Clinical Research Centers Program

The General Clinical Research Centers (GCRCs) Program, initiated in 1960 and administered by DRR, now part of the NCRR, supports a nationwide network of 78 centers for clinical research within hospitals of academic medical institutions. At these centers multicategorical clinical research is conducted on many common and rare diseases. The GCRCs are usually discrete units within major hospitals. They provide an infrastructure for clinical research by investigators who receive their primary funding for research from components of the NIH other than the NCRR. As a result, the research carried out in the GCRCs reflect the missions of several NIH institutes including cancer, heart disease, infectious diseases, diabetes, neurological diseases, obesity, arthritis, and aging. GCRCs also provide a hospital's resident physicians and medical students the opportunity to learn and participate in the translation of basic and clinical research findings into established medical practice. Clinical evaluations at the GCRCs focus predominantly on phase I and early phase II trials of new drug treatments and other aspects of therapy. Prevention research includes studies of immunizations, control of blood pressure, dietary lipids, smoking habits, infectious and toxic agents, and alcohol and drug abuse.

Several nutrition-related research highlights from the GCRCs program follow:

- **Osteoporosis and the Parathyroid Gland**
Evidence of reduced activity by the parathyroid glands of postmenopausal

women with osteoporosis has been detected by investigators at the Columbia University College of Physicians and Surgeons GCRC in New York City. The findings suggest new strategies for treating this disorder, which in later life affects an estimated 25 to 30 percent of all white women in the United States. The disease, characterized by loss of bone tissue mass, is far rarer among elderly black women. Males, both white and black, are much less susceptible than their female counterparts. When the Columbia University investigators administered phosphate to postmenopausal women who were free of osteoporosis, the women's parathyroid glands secreted large amounts of a hormone that increases bone calcium. By contrast, postmenopausal women with osteoporosis showed a diminished hormonal response to phosphate treatment, suggesting a defect in parathyroid functioning. Since this apparent parathyroid abnormality may contribute to the development of osteoporosis, the investigators suggest that therapeutic efforts might be directed toward increasing the parathyroid gland's capacity to regulate calcium and thus compensate for bone loss associated with this progressive, disabling condition that often contributes to death in the fragile elderly.

- **Preventing Spinal Fractures**

Osteoporosis affecting the spine strikes about 5 million Americans, primarily postmenopausal women, making them susceptible to spinal fractures and curvature related to weakened vertebrae, back pain, and gastrointestinal distress. About one-half million spinal fractures are recorded in the United States annually.

At the University of Texas Southwestern Medical Center GCRC in Dallas, clinicians have reported a new approach to treating spinal osteoporosis. The treatment consists of a new slow-release form of sodium fluoride combined with a calcium citrate supplement—a combination that increases bone mass and remineralizes bone. The new

therapy regimen is directed toward patients who have already sustained substantial loss of bone and who are at risk of developing spinal fractures. Conventional treatments using estrogen and calcium supplements are given early in the postmenopausal period and represent an effort to prevent the development of osteoporosis.

At the Dallas GCRC more than 300 patients with spinal osteoporosis have received the combination treatment for an average period of 3.5 years. The GCRC investigators found that bone density in the lumbar spine either increased or stabilized in all patients after treatment. On average, the improvement represented an increase of more than 5 percent in bone mass each year for up to 4 years. Biopsies showed the new bone to be mineralized normally. Adverse complications were minor. Fewer than 5 percent of patients had gastrointestinal complications; rheumatic complications also were infrequent.

The new treatment represents a significant improvement over conventional therapy with fluoride, which often results in gastrointestinal problems and bleeding, rheumatic complications including stress fractures, and the formation of weak, abnormal bone tissue.

- **Lipoprotein Lipase and Female Obesity**

The enzyme lipoprotein lipase appears to play a key role in obesity, according to studies conducted at GCRCs in the University of Colorado Health Sciences Center in Denver and the University of Utah School of Medicine in Salt Lake City. Lipoprotein lipase regulates the storage of dietary fat. Situated on the walls of blood capillaries, it splits dietary fat into triglycerides associated with chylomicrons (fat-containing particles) and very-low-density lipoproteins. The resulting free fatty acids and monoglycerides may be taken up by cells and further processed, either for energy functions or for reversion to fat (triglycerides) to be stored in adipose tissue.

In the Colorado investigation six normal-weight women and nine obese women were given intravenous infusions of combined glucose and insulin—which stimulate the enzyme’s activity—over two separate 6-hour periods. During one of the 6-hour infusions participants ingested fat in the form of corn oil, which suppresses lipoprotein lipase. The researchers measured lipoprotein lipase activity in small samples of fatty tissue removed from the women’s buttocks before and after administration of glucose and insulin as a basis for subsequent comparison.

The obese women were then enrolled in a supervised weight-loss program. After they had maintained a weight loss for 3 months their enzyme activity was measured again. Investigators found that fasting levels of lipoprotein lipase were significantly higher in obese and reduced-obese women than in lean women.

Although lipoprotein lipase activity in normal women increased during insulin-glucose infusion alone, it showed no increase when the infusion was preceded by an ingestion of corn oil, which suppressed the enzyme activity. The obese women, however, showed no change in their lipoprotein lipase activity in response to insulin-glucose infusion with or without corn oil. In contrast, reduced-obese women showed a significant increase in lipoprotein lipase after the glucose-insulin infusion, and this effect was not altered by the ingestion of corn oil.

The findings suggest that a metabolic adaptation to weight loss occurs in obese women who lose weight and maintain their reduction for at least 3 months. In these women fat no longer has the ability to inhibit lipoprotein lipase. The findings support the theory that human adipose tissue establishes its own "set point" to regulate fat deposition and uses mechanisms such as increased lipoprotein lipase activity to help regain lost fat soon after it is lost. For dieters the finding supports a perception

that their main challenge is to avoid regaining weight in the days or weeks immediately after weight loss, particularly within the first 3 months.

Studies at the University of Washington (Seattle) GCRC and the University of Utah School of Medicine in Salt Lake City have explored in obese women the relationship between plasma sex steroid hormones and lipoprotein lipase. The results of that study suggest that the female hormone estradiol is a major negative regulator of lipoprotein lipase activity in these women.

Investigators at the University of Washington also have shown high levels of lipoprotein lipase activity in reduced-obese women.

- **New Data on Breast Milk**
GCRC-based investigators at the University of Colorado Health Sciences Center in Denver measured the transfer of human breast milk to newborn infants and found that each infant-mother pair they studied had a characteristic milk volume that was significantly related to infant weight at 1 month of age.

An extremely low transfer of milk from mother to offspring was observed on the first and second days after birth. However, milk transfer rose rapidly between the third and fifth days, then continued to rise slowly to a maximum of about 800 grams a day by the sixth month, when introduction of solid foods into the infant’s diet may be appropriate. In addition, the Denver group analyzed milk for components such as proteins, carbohydrates, fats, electrolytes, and trace elements. The investigators found that neither milk volume nor the major components of milk—protein, carbohydrate, fat, and water—was affected by 21 hours of maternal fasting. The study also revealed that breast milk, although genuinely considered "the gold standard" for infant feeding, cannot immediately correct low blood sugar on an infant’s first

or second day of life, because the volume of milk consumed is so low.

The volume of breast milk consumed by the infant varied over time, however, as did its zinc, copper, and manganese content. That information will undoubtedly influence development of infant formulas and supplements.

- **Dietary Patterns of Old and Young Adults**
Elderly men and women in good health prefer a lower-calorie diet containing fewer carbohydrates and less fat than do healthy young people, according to a study conducted at the Massachusetts Institute of Technology GCRC in Cambridge. Investigators also reported that the older people in the study snacked less often and were more active than the young adults. The findings were based on rigorously monitored food intakes of young and old persons who lived for 4 days in an identical, controlled environment at the GCRC.

Each day the young people consumed 300 to 600 kilocalories more than did the elderly men and women, as determined by calorie-counted meal choices of known composition and snacks available from a refrigerated vending machine interfaced to a microcomputer. The elderly consumed almost 85 percent of their total calories from meals, the young people only 72 percent. The balance came from snacks, mostly carbohydrate-rich foods. The elderly ate an average of 2.2 snacks each day, less than half the number, 4.5, eaten by the young.

During the study each participant's motor activity was measured 24 hours a day by a solid-state activity monitor worn like a wrist watch. The older people were more active, taking walks and otherwise keeping busy; the young people spent a great deal of time loafing and watching television.

The investigators say that the study does not define whether or not elderly people in

nursing homes have altered patterns of eating or snacking.

Nutrition Research in Other Centers

The center mechanism has proven useful in providing support for long-term multidisciplinary programs of research and development in critical health problem areas. Nutrition research is an important component of the programs of many of the centers supported by the NIH. Highlights of nutrition research conducted at a variety of specialized centers include the following:

- **Obesity Core Center at St. Luke's-Roosevelt Institute for Health Sciences** (supported by NIDDK)

The aim of the Obesity Core Center is to foster interdisciplinary cooperation of a group of investigators conducting programs of high quality research related to obesity. Examples of the topics of ongoing studies include ethnic specificity in new and old models of body composition, food intake control by cholecystokinin in obesity, the effect of exercise on food intake, body protein loss during severe caloric restriction, the impact of body fat mass and percent fat on metabolic rate and thermogenesis, and the thermic effect of constant and relative caloric loads in lean and obese subjects. Researchers at the center have recently established the usefulness of dual-photon absorptiometry for the measurement of body fat, found that males have more alpha fat receptors (indicative of antilipolytic activity) than beta fat receptors (indicative of lipolytic activity) in the abdominal region, and determined that resting metabolic rate is related to fat-free mass and is not independently related to obesity, while the impaired thermic effect of food in obesity is specifically a function of relative fatness rather than fat mass per se.

- **Nutrition and Chronic Disease CNRU at the University of San Francisco** (supported by NICHD)

This program is a multidisciplinary, inter-institutional project concerned with the relationship of nutrition and chronic disease. Core laboratories are dedicated to nutrition and metabolism, radio-immunoassay, tissue culture, and biochemical analysis. Areas of interest include nutritional requirements, nutritional deficiencies, and assessment of nutritional status in renal, liver, neurological, and gastrointestinal disorders; diabetes mellitus; obesity; and hematological disease. Ongoing research projects include an examination of zinc homeostasis in pregnant diabetic women, a study of Megace therapy and weight gain in patients with AIDS, a survey of risk factors for noninsulin-dependent diabetes among Australian aborigines, and an analysis of factors related to the development of infant macrosomia.

- Chemosensory Clinical Research Center at the Monell Chemical Senses Center, University of Pennsylvania Smell and Taste Center, and Connecticut Chemosensory Clinical Research Center, University of Connecticut Health Center (supported by NIDCD)

The activities of the clinical chemosensory research centers include nutritional management to rehabilitate or maintain the quality of life in patients with taste or smell disorders. The nutritional assessment of the patients with appropriate dietary intake measurements, dietary and weight history, food behavior questions, and anthropometric measures enables nutritionists to identify potential nutritional problems and to provide guidance for dietary behavior modification.

- Core centers for research in mental retardation at the University of California, Los Angeles; the University of Colorado Health Sciences Center; and the Kennedy Institute for Handicapped Children in Baltimore (supported by NICHD)

The centers provide central support for a multifunded, interdisciplinary research and training program in mental retardation. Nutrition-related research conducted at these centers has included investigations of the effects on brain development of chronic undernutrition over several generations; the development of a hypoketonemic animal model through dietary manipulation; studies of the role of trace metals, especially copper, zinc, and chromium, as well as undernutrition and environmental deprivation, in brain development; studies on the efficacy of an arginine restricted diet in further progression of chorioretinal degeneration in patients with gyrate atrophy; and investigations of treatment with low tryptophan diets and specific serotonin antagonists on feeding, sleeping, and other behaviors in patients with urea cycle enzymopathies.

- Centers for research in the environmental health sciences at the University of Medicine and Dentistry of New Jersey--R.W. Johnson Medical School; the University of California, Berkeley; the University of Rochester; and the University of Cincinnati (supported by NIEHS)

The programs of these centers are intended to enhance the understanding of environmental hazards affecting human health. Nutrition-related research conducted in the various centers includes toxic and essential metals, nutritional impact on toxicity and carcinogenesis, and dietary exposure to toxic substances.

Examples of other centers which include a nutrition research component include the following:

- Specialized Centers for Research in Arteriosclerosis at Wake Forest University; the University of California, San Diego; the University of California, San Francisco; the University of Iowa; and the University of Chicago (supported by NHLBI)

- The Regional Dental Research Center at the University of North Carolina, Chapel Hill; the Rochester Caries Research Center at the University of Rochester; and the Specialized Caries Research Center at the Forsyth Dental Center, Boston (supported by NIDR)
- Centers for the study of liver disease at the University of California, San Francisco; the University of Minnesota of Minneapolis-St. Paul; and Yeshiva University (supported by NIDDK)
- Diabetes-Endocrinology Research Centers and Diabetes Research and Training Centers (supported by NIDDK)
- Perinatal Research Emphasis Centers (supported by NICHD)
- The Center for Research on Developmental Disabilities at the University of Minnesota of Minneapolis-St. Paul (supported by NICHD)
- Centers for research in reproductive biology/physiology at the University of Pittsburgh and Vanderbilt University (supported by NICHD)
- Centers for burn/trauma research at the Cornell University Medical Center, New York, and Brigham and Women's Hospital, Boston (supported by NIGMS)

Nutrition Research in the Animal Resources Program

Regional Primate Research Centers Program

The NCRR supports seven Regional Primate Research Centers (RPRCs) established nearly 30 years ago through the Animal Resources Program. These centers provide a major scientific resource of regional, national, and international importance to biomedical research. The RPRCs continue to provide for the development and study of nonhuman primate animal models that are essential for clinical and basic research on the mechanisms

and processes underlying human diseases and health problems.

The RPRC program provides specialized facilities, nonhuman primate resources, and appropriate research environments for many types of biomedical studies. The NCRR provides funds to support basic operations and research activities at these centers, which is complemented by awards for specific research projects from the NIH categorical institutes, other Federal agencies, and private foundations.

Highlights of nutrition research activities at two of the RPRCs are described below:

- **Nutritional Importance of Omega-3 Fatty Acids**

Several investigators at the Oregon Regional Primate Center in Beaverton are studying the role of dietary omega-3 fatty acids in the development of the retina and brain, tissues that normally contain especially high levels of omega-3 fatty acids. In the diet, omega-3 fatty acids are found in fish, certain vegetables, and human milk.

Diets very low in omega-3 fatty acids were fed to rhesus monkeys during pregnancy and to their infants from birth. As a result, infant animals had greatly reduced amounts of omega-3 fatty acids in the brain and retina, visual acuity was reduced by 50 percent at 2 to 3 months of age, and the retina showed abnormal physiological responses to light. Differences in the behavior of these monkeys, including increased stereotypic behaviors and increased repetitive errors in a learning task, have now been found. Furthermore, the deficient monkeys show abnormally high fluid intake and excretion. The underlying physiological or behavioral reasons for this effect now are being studied.

The investigators also are examining the effects of postnatal omega-3 fatty acid deficiency, rather than the combination of prenatal and postnatal deprivation studied

previously. In infant animals deprived from birth, the level of omega-3 fatty acids had decreased 50 percent in the cerebral cortex by 7 months of age, and changes were seen in physiological responses of the retina. These studies are particularly relevant to the composition of human infant formulas, some of which contain low levels of these fatty acids. The results of this study suggest that infant formulas should provide amounts of omega-3 fatty acids equivalent to those in human milk.

- **Effects of Obesity on Maternity and Child Health**

Researchers at the Wisconsin Regional Primate Research Center in Madison are investigating the relationship between natural metabolism and fetal development in the rhesus monkey. Studies on these relationships are difficult to accomplish during human pregnancies for ethical and practical reasons. Therefore, because of the similarities between human and rhesus monkey pregnancies and the dissimilarity of other laboratory animal species, this animal represents the best model for studying the effects of maternal metabolism on fetal development.

Pregnancy for obese women is often complicated by high blood pressure, toxemia, carbohydrate intolerance, and difficulties in giving birth. Obese mothers are also more likely than others to have infants who are large for gestational age and subject to neonatal complications. These infants, particularly those born to mothers who have diabetes mellitus during pregnancy, may have a greater risk of becoming obese and of developing glucose intolerance later in life.

To understand the complications of pregnancy in obese women, investigators at the Wisconsin center analyzed approximately 100 well-controlled rhesus pregnancies. The pregnant monkeys were given glucose tolerance tests during the final trimester of pregnancy and also before and

after pregnancy. The animals' weight and fatness were measured, as was the size of their offspring at delivery. This work led to five conclusions:

- Increasing obesity of the nonpregnant monkeys was accompanied by insulin resistance. This was generally characterized by fairly normal glucose levels but elevated insulin levels, both fasting and stimulated.
- Rhesus pregnancy also was accompanied by elevated insulin levels. The hyperinsulinemia of pregnancy was probably secondary to an interference with the effectiveness of insulin by progesterone or other hormones of pregnancy.
- Prevailing glucose levels in the "average pregnancy" tended to be lower than in the same animal when nonpregnant, due to use of glucose by the fetus and placenta.
- Obesity at the time of conception was associated with a greater chance of developing glucose intolerance during pregnancy. It appeared as if the fatter mothers were unable to cope with the combined stresses of increased obesity plus pregnancy.
- Even mildly impaired glucose tolerance during pregnancy resulted in increased fetal growth. This increased growth was probably a consequence of fetal overnutrition and stimulation of fetal growth factors.

In extreme cases such as overt maternal diabetes mellitus during pregnancy enhanced fetal growth is associated with a host of perinatal complications and also may produce long-term complications for the physical and psychological development of the offspring. Rhesus monkeys represent a valuable model for further study of the mechanisms of these problems as well as for possible therapies.

HIGHLIGHTS OF NUTRITION RESEARCH: INTERNATIONAL NUTRITION RESEARCH ACTIVITIES

The NIH's participation in international activities includes projects undertaken

intramurally, by NIH staff or visiting foreign scientists, or extramurally, by NIH grantees collaborating with foreign colleagues or by scientists in other countries. Some of these efforts are conducted through bilateral agreements between the United States and another government. International activities also include NIH participation in meetings, conferences, and workshops that often evolve into long-term relationships between scientists and organizations of various nationalities.

The focal point for coordinating and promoting biomedical research between the NIH and foreign countries is the Fogarty International Center (FIC). The FIC facilitates the assembly of scientists in the biomedical, behavioral, and related fields; promotes international collaboration in the life sciences through its research programs, conferences, and seminars; provides postdoctoral fellowships for research in the United States and abroad, and promotes biomedical scientist exchanges between the United States and other countries; coordinates NIH activities in the health sciences that reach international level; and serves as a central resource for foreign scientists and visitors at the NIH. The FIC maintains contacts with multinational organizations such as the World Health Organization (WHO) and the Pan American Health Organization (PAHO).

Below are some examples from the ICDs of highlights of recent scientific advances related to nutrition resulting from international activities and collaborations. Descriptions of some of the activities listed below and additional international activities can be found in section 2.

- In an NCI-supported activity, investigators are pursuing studies in Linxian, China, to clarify the ability of multiple vitamin-mineral supplements to help prevent esophageal cancer mortality.
- In Tanzania, NCI is sponsoring the conduct of phase-II randomized clinical trials with albinos to determine the efficacy of beta-

carotene in arresting, inhibiting, or reversing the abnormal clinical and pathological progress of skin changes caused by skin cancer.

- In Finland, the ATBC Lung Cancer Prevention Study is a large phase III trial of beta-carotene and alpha-tocopherol supplementation for the prevention of lung cancer among older male smokers. NCI-supported researchers also are assessing the role of fats, selenium, and vitamins A, E, and C in breast cancer development. In addition, they are evaluating the relation of nutrient intake to subsequent cancer development, particularly of the breast, colon, and lung.
- The NEI is sponsoring case-control studies in India, Italy, and the United States to explore possible personal and environmental risk factors for aging-related cataract. The results of the data analysis from India so far indicate that an increased risk of cataract can be associated with certain blood levels of some nutrients. The researchers will study intercountry comparisons when the data from the other studies become available.
- NEI is consulting on a recently completed field project sponsored by the Ford Foundation of India at the Aravind Eye Hospital in Madurai, southern India. Investigators are analyzing the data to determine the effectiveness of frequent, low-dose supplements of vitamin A on the incidence and severity of clinical vitamin A deficiency and other morbidities and on mortality trends.
- NEI is providing technical oversight to the Office of International Health for an AID-sponsored operations research project by the University of Michigan in Nepal. The project seeks to determine the most cost-effective means of reducing the prevalence of vitamin A deficiency in Nepalese children. Interventions that are being compared include distribution of high-dose vitamin A capsules four or six times monthly, high-dose capsule distribution

with public health measures to control infections, versus nutrition/health education combined with public health measures to control infections.

- The north and northeast of Thailand have long been considered nutritionally vulnerable areas. Subclinical vitamin A depletion is suspected but not well documented. NEI is providing consultative advice to the Ministry of Public Health through an AID grant for a survey of these areas to detect subclinical vitamin A depletion. The survey is being conducted during both the rainy and dry seasons.
- Since 1981, U.S. and Chinese scientists have collaborated on large-scale epidemiological studies, jointly supported by the NHLBI and the PRC ministry of health, that compare trends, rates, and risk factors for cardiopulmonary disease. The investigators are studying more than 11,000 workers from 4 populations in Beijing and Guangzhou. A baseline survey was completed in 1986. Participants were rescreened in 1987. When the phase II data were compared with the phase I data the researchers found that all Guangzhou population subgroups had significantly increased their mean serum levels of total cholesterol, LDL-cholesterol, and triglycerides during the interim period. These results suggest an unfavorable lifestyle trend in the Guangzhou area. Similar trend analyses must be completed for data from North China before investigators can determine whether a similar shift in blood lipids has occurred among the study's Beijing participants. Based on the unfavorable risk factors profile of Beijing workers, intervention studies are being carried out to reduce smoking, salt intake, and elevated blood lipids, high blood pressure, and obesity in certain groups of workers.
- In the Federal Republic of Germany, NHLBI has collaborated with German investigators to test the ability of a concerted intervention strategy to modify cardiovascular risk factors in German communities. The risk

factors intervened against include hypertension, elevated blood cholesterol, cigarette smoking, overweight, and lack of exercise. Last year, U.S. and German experts met to discuss joint analyses of the intervention program results and health survey data.

- Because patterns of cardiovascular disease vary greatly in the United States and Japan, the two countries have a unique opportunity for comparative studies and new insights into the disease's causes. In FY 1989, NHLBI continued to support an agreement for scientists to exchange joint research such as blood pressure and other cardiovascular risk factors among children and young adults and community intervention and prevention of cardiovascular disease. The intervention programs have increased awareness of risk factors and knowledge about health promoting behaviors in both countries.
- Joint scientific research agreements between the NHLBI and the U.S.S.R. since the early seventies have allowed for collaborations in nutrition research areas. These have centered on epidemiologic studies of cardiovascular disease risk factors, morbidity and mortality. Basic and clinical research on the effects of lipoproteins on atherosclerosis and joint hypertension studies between the two countries have allowed for better understanding and control of these disorders. In addition, joint research in the areas of cardiopulmonary epidemiology and prevention continue, with the U.S. and the U.S.S.R. collaborating on epidemiological studies of primary prevention of hypertension in children and health education in these countries, in areas such as hypertension and cholesterol.
- Joint research between the United States and Poland began in 1974. A major focus of this NHLBI collaboration is to determine the reasons for opposing trends in cardiovascular diseases (CVD) observed in the two countries; CVD has declined in the United States whereas it has increased by about 40 percent in Poland over the past

decade. Comparisons in trends in risk factors, including extensive dietary information, and mortality data are currently under way. The bases for these comparisons are the Pol-MONICA study, (U.S.) ARIC and (U.S.) LRC Prevalence study.

- Rotaviruses are the most important group of etiological agents in producing severe diarrhea among infants and young children in industrialized and poor countries. Using a vaccine developed by NIAID, researchers conducted field trials in Burma, Chile, Finland, Israel, Sweden, United States, and Venezuela. So far, the most promising results were from Venezuela, where overall vaccine efficacy was 90 percent. Efforts are continuing to develop variations of this vaccine and test their effectiveness against other types of human rotavirus.
- Researchers from NIAID and Bangalore, India, are investigating the diagnosis and treatment of adverse reactions to foods and additives. Researchers have completed a clinical study to determine the reproducibility of allergic reactions to aspartame, the non-nutritive sweetener. So far, the researchers only have noted two mild reactions to the sweetener.
- The NIAMS continues to collaborate with Italian researchers in designing national epidemiological studies in various regions of Italy on osteoporosis. In preliminary analysis of fracture-mortality data, age-adjusted rates for deaths attributed to limb fractures were significantly higher in the northern and central regions than in the southern regions. There also appears to have been a significant and steady increase in the age-specific rates of deaths attributed to femoral fractures in Italy in 1961, 1971, and 1981. The researchers will continue to explore these observations in future multiregional studies.
- For more than two decades NICHD has participated in a collaborative research program on malnutrition with Japan. The research objectives of this joint effort include ascertaining the effects of changing food patterns on disease, and determining the effects of malnutrition during pregnancy, infancy, and childhood on lactation, reproduction, work performance, and social competence.
- NIDR continues to participate in conjunction with WHO on the International Collaboration for Oral Health Research. At an international workshop last year, dental scientists from around the world presented their research priorities for international collaboration in a range of scientific areas including nutrition. NIDR staff members now are working to implement the report's recommendations.
- The nutritional status and oral development of 200 Peruvian children is under study by NIDR scientists. The study showed that infants who suffer malnutrition in their first year of life are extremely susceptible to decay in the first set of teeth, which may be due to poorly mineralized tooth enamel. These results have important implications for assessing nutrition's role in oral health.
- NIDDK researchers continue to collaborate on the U.S.-Japan Malnutrition Panel, which is part of the U.S.-Japan Cooperative Medical Sciences Program. The Panel was created to conduct research that could help alleviate malnutrition, especially in Southeast Asia. The two countries have established four goals to emphasize in their collaborations: nutritional aspects of bone disease, including the interrelationships of osteoporosis, calcium, and the influence of other nutrients and the aging process; nutritional significance of unsaturated fatty acids in health and disease; endogenous mediators of inflammation, infection, and malignancy, and their effects on nutritional metabolism; and sulfur amino acid metabolism and nutrition. Two recent studies supported in association with the U.S.-Japan Malnutrition Panel were studies of

osteoporosis in premenopausal and postmenopausal women in Kobe and studies on the effects of eicosapentaenoic acid on liver metabolism and on fatty acid metabolism in isolated liver cells.

- NIDDK continues its collaboration with India on an epidemiological study on the formation of urinary tract stones. The goals of the study related to nutrition include clarifying differences between upper and lower urinary stones with respect to environmental and nutritional influences, and correlating a stone's composition and morphological appearance with a specific metabolic and endocrine profile and with nutritional and dietary influences. The project ultimately should establish the incidence and prevalence of kidney and bladder stones in India.
- NIEHS joint research conducted under the U.S.-Japan Cooperative Medical Sciences Program on the formation of mutagens in food has attracted worldwide interest. In the past several years, survey-type experiments have revealed the presence of mutagenic chemicals in a wide range of foods and beverages. Researchers are examining how some of these food mutagens are produced. These studies may provide a better understanding for the prevention of cancer and genetic diseases in which diet is a contributing factor.
- This year, scientists from the Institute National de la Sante et de la Recherche Medicale laboratory in Lyon, France confirmed the accuracy and reliability of a prenatal diagnostic test developed by NINDS scientists. The test, chorionic villus biopsy, allows early diagnosis of Niemann-Pick disease type C, a fatal genetic lipid storage disorder that prevents children from properly metabolizing cholesterol. NINDS scientists developed the procedure for analyzing cholesterol accumulation in biopsy specimens, while the French investigators applied the procedure to chorionic villus biopsy for early prenatal diagnosis.

- Scientific exchange between NIA researchers and Italy continues under the U.S.-Italy Science and Technology Agreement. The second Joint Conference on Aging will be held in December 1990, during which representatives from the National Council for Research of Italy, the National Center for Health Statistics and the NIH will exchange information about epidemiologic methodologies for studying nutrition and sensory impairments in the elderly.
- NIA continues its lead role in the WHO Special Program for Research on Aging (SPRA), designing protocols for four comparative population studies: age-associated dementias, osteoporosis, determinants of healthy aging, and immune function in the elderly.

HIGHLIGHTS OF NUTRITION RESEARCH: NATIONAL NUTRITION MONITORING

The National Nutrition Monitoring System includes all Federal surveys and surveillance activities designed to collect health and nutritional status measurements, food and nutrient consumption measurements, food composition measurements, dietary knowledge and attitude assessments, and food supply determinations. The NIH provides direct support to a variety of national nutrition monitoring activities, as well as supporting the science base that undergirds much of the monitoring system. Some examples of NIH contributions to national nutrition monitoring research are cited below.

National Health and Nutrition Examination Surveys

To assess the nutritional status of Americans, particularly as related to health and mortality outcomes, a series of National Health and Nutrition Examination Surveys (NHANES) was begun in 1971. Conducted during 1971 through 1974 and 1976 through

Survey/Surveillance Activity (Sponsoring Agency/Agencies)

National Health and Nutrition Examination Survey (NCHS)
National Health Interview Survey (NCHS)
NHANES I Epidemiologic Followup Study (NCHS)
National Maternal and Infant Health Survey (NCHS)
National Mortality and Natality Followback Survey (NCHS)
Vital Statistics System (NCHS)
National Hospital Discharge Survey (NCHS)
National Ambulatory Medical Care Survey (NCHS)
National Nursing Home Survey (NCHS)
Pregnancy Nutrition Surveillance System (CDC)
Pediatric Nutrition Surveillance System (CDC)
Surveillance of Severe Pediatric Undernutrition (CDC)
Behavioral Risk Factor Surveillance System (CDC)
Nutritional Evaluation of Military Feeding Systems and Military Populations (USARIEM)
Nutrition Status Surveys and Surveillance Systems (AID)
Nationwide Food Consumption Survey (HNIS)
Continuing Survey of Food Intakes by Individuals (HNIS)
Total Diet Study (FDA)
Vitamin and Mineral Intake Survey (FDA)
Survey of Infant Feeding Patterns (FDA)
Food Label and Package Survey (FDA)
National Nutrient Data Bank (HNIS)
Nutrient Composition Laboratory (ARS)
Health and Diet Survey (FDA and NHLBI)
Survey of Weight-Loss Practices (FDA and NHLBI)
Diet-Health Knowledge Survey (HNIS, FSIS, and FDA)
Cholesterol Awareness Survey—Public Survey (NHLBI and FDA)
Cholesterol Awareness Survey—Physicians' Survey (NHLBI)
Nationwide Survey of Nurses' and Dietitians' Knowledge, Attitudes, and Behavior Regarding Cardiovascular Disease Risk Factors (NHLBI)
Basic Office of Cancer Communications National Knowledge, Attitude, and Behavior Survey (NCI)
Cancer Prevention Awareness Survey (NCI)
Prospective Survey of Infant Feeding Practices Among Primipara (NICHD)
Food and Nutrient Supply Series (ERS and HNIS)
A.C. Nielsen Scantrack (ERS, HNIS, AMS, FNS, FSIS, and FDA)
Food Needs Assessment Project (AID)
Consumer Expenditure Survey (Bureau of Labor Statistics)
Survey of Income and Program Participation (Bureau of the Census)

1980, respectively, NHANES I and II constituted the largest in-depth national surveys, until now, of health and nutrition ever made on representative samples of the U.S. population. NHANES III, scheduled to run from 1988 through 1994, will provide much-needed updating of this critical information. Conducted by the National Center for Health

Statistics (NCHS), the NHANES consists of a series of surveys of probability samples of the population, each comprising over 20,000 U.S. residents. The surveys include physical examination, anthropometry, blood cell assessments, biochemical analyses of blood and urine, x-rays, functional assessments, health histories, and dietary intake interviews. The

resulting data provide national estimates of diseases and of health and nutritional characteristics of the U.S. population and selected subgroups. Additionally, NHANES I respondents are traced and reexamined in a longitudinal follow-up study; information is obtained from hospital records, the National Death Index, and death certificates.

NHANES III also has been planned as a longitudinal study with morbidity and mortality end points. The survey will "oversample" older persons. (That is, approximately 7,000 persons aged 60 years and older will be included; of this group, about 1,000 will be aged 80 and older.) For the first time, NHANES III is collecting health and dietary information on the very old (age 75 and older), yielding a comprehensive resource for aging research. Blacks, Mexican Americans, and Puerto Ricans will be heavily represented in the general survey.

The NIH supports NHANES in several ways. NIH-supported scientists participate in the planning of each NHANES survey. The NIH devotes research funds to improving methods and techniques of measuring dietary intake, to fine-tuning biochemical and clinical indices of nutritional status, and to perfecting other assessment and monitoring parameters. Each year NIH institutes fully or partially support NHANES follow-up surveys. During the years of the survey itself, NIH institutes fund both the survey and follow-up activity.

Eight NIH institutes (NCI, NHLBI, NICHD, NIDR, NIDDK, NIAID, NIA, and NIAMS) contribute to NHANES regularly. The NIA is collaborating with the NCHS to fund acquisition of additional dietary intake information and collection of health and dietary information on a longitudinal basis from older participants. The NHLBI is funding lipoprotein analysis and survey measurements that assess cardiovascular risk factors. The NICHD supports methodology to investigate growth relationships and dietary intake. The NIAMS supports aspects of the survey related to arthritis, osteoporosis, and skin diseases.

The NIDDK funds measurements related to gallstones, kidney disease, and diabetes. The NIDR continues to fund the oral health examination and questionnaire component.

The NIA in conjunction with the NCHS is conducting a follow-back study of the NHANES III to collect additional nutrition data from the respondents over 60 years of age beyond that included in the main body of the NIA-NCHS interagency agreement for the NHANES III. The follow-back study will collect two additional 24-hour dietary recalls in addition to the single 24-hour recall and the non-quantitative food frequency that will be administered to all subjects. The two additional recalls will be administered by telephone, using the same computerized techniques used for the in-person recall obtained in the NHANES mobile examination centers (MECs). In addition to obtaining intake data on foods, beverages, and dietary supplements consumed the day before, the MEC interview will be used as a training session for the subsequent telephone interviews. The three recalls per person will be patterned to account for seasonal and weekly variations in eating habits.

The NIH derives significant research advantages from NHANES data. Various institutes perform follow-up studies using NHANES data to test hypotheses about the relationship of dietary practices to the incidence of cancer, heart disease, obesity, osteoporosis, and kidney disease, as well as to assess diets and to study the effect of diet on overall health and longevity. Extramural researchers supported by NIH also make extensive use of NHANES data. For example, researchers are currently using NHANES data in the conduct of studies on:

- The impact of living arrangements on dietary status in U.S. adults.
- The proximate determinants of low birth weight and infant mortality in black, white, and Hispanic women.

- Secular trends in cardiovascular risk factors in the adolescent and adult U.S. population.

Other NIH-Supported Nutrition Surveys

In addition to the NHANES series, the NIH supports or undertakes other valuable nutrition surveillance efforts. The following are a few recent examples:

- Cholesterol Awareness Surveys (NHLBI and FDA), conducted among physicians and other U.S. adults, 1983, 1986, and 1990.
- Nationwide Survey of Nurses' and Dietitians' Knowledge, Attitudes and Behavior Regarding Cardiovascular Risk Factors (NHLBI), to be conducted among U.S. nurses and dietitians.
- Vitamin/Mineral Supplements in Cancer Control (NCHS and NCI), 1988.
- Physician Knowledge Survey on Hypertension (NHLBI), 1978-1988.
- Basic Office of Cancer Communications National Knowledge, Attitude, and Behavior Survey (NCI), 1988-1991.
- Cancer Prevention Awareness Program (NCI), conducted among U.S. adults, started in 1983 and is ongoing.

Composition Methodology

In order to fill potential gaps in the information provided by other agencies, several NIH institutes undertake studies which include analysis of the nutritional content of food. A few such examples include:

- Dietary fiber and fiber components, carotenoids, vitamin A, and selenium analyses (NCI).
- Taurine, pyridoxine beta glucoside, molybdenum, and biotin analyses (NIDDK).

- Development of methods for determining nutrients in human colostrum and milk (NICHD).
- Mutagens from the cooking of foods (NIEHS).
- Food fatty acid analysis and evaluation (NHLBI).
- USDA Services for Nutrient Composition Laboratory (NHLBI). This interagency agreement supports the development of new or improved techniques for the analysis of nutrients, especially lipids, carbohydrate fractions, trace minerals, and amino acids.

Computerized Nutrient Data Sources

Examples of NIH-supported nutrient data bases include the following:

- USDA Nutrient Data Bank. The NHLBI supports the continued development of the USDA Nutrient Data Bank and the USDA revision of Agriculture Handbook No. 8, Composition of Foods, Raw, Processed, Prepared. Funds are specifically directed to the compilation of accurate food composition data for nutrients associated with heart, lung, and blood diseases (lipids, carbohydrate fractions, trace elements, and amino acids).
- Nutrition Coordinating Center. The NHLBI supports a standardized system at the University of Minnesota for collecting, coding, processing, and analyzing dietary information. The information in the interactive computer data base comes from the USDA, other standard references, and food manufacturers. The coding manual and nutrient data base are continually updated by a staff of nutritionists and data specialists to reflect changes in the marketplace. This system has been field tested extensively in studies throughout North America since 1974.

- Food Component Research Data Base. The NCI in collaboration with the FDA, as well as several European countries, are adapting and extending the Factored Food Vocabulary (FFV) into a standardized description of food items in the world food supply. A prototype food component research data base, indexed by the FFV, and containing numeric and bibliographic data on the content of nutrients, additives, contaminants, and naturally occurring substances in foods, is being developed in consultation with a number of international experts. This comprehensive data system will provide a valuable research tool for investigators conducting dietary interventions, clinical trials, and epidemiological studies on the relationship between dietary components and cancer risk and will serve as a resource of information which is essential for the formation of public policy on diet-related public health issues.

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Section 4. Financial Report of Biomedical Research and Training in Nutrition



FINANCIAL REPORT OF BIOMEDICAL RESEARCH AND TRAINING IN NUTRITION

THE LEADER IN FEDERALLY SUPPORTED NUTRITION RESEARCH AND TRAINING

In FY 1989, the NIH led all Federal agencies in financial support of nutrition research and training, for a total of \$287 million. This total represents the combined individual contributions of the 13 NIH institutes, 2 centers, and 1 division that supported biomedical nutrition research and training. Actual obligations for FY 1989 biomedical nutrition research and training for all NIH ICDs as amounts and as percentages of their total obligations are shown in table 1. Leading the

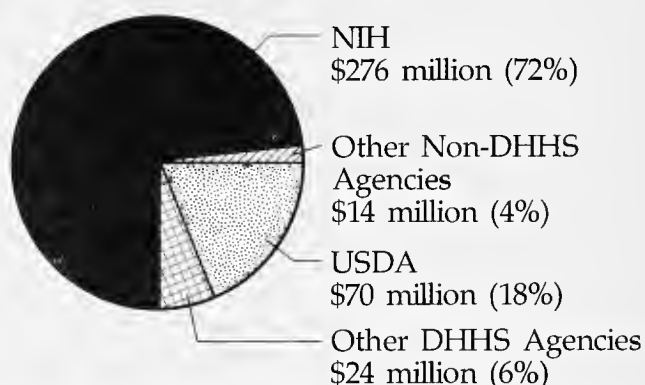
ICDs in total dollars expended in support of nutrition research were NCI, with \$64.5 million; NHLBI, with \$64.3 million; NIDDK, with \$64.0 million; NICHD, with \$31.2 million; and DRR, with \$23.8 million. Leading NIH components in terms of the percentage of total budget of each ICD dedicated to the support of nutrition research and training were NIDDK, with 11.4 percent; NICHD, with 7.3 percent; DRR, with 6.2 percent; and NHLBI, with 6.1 percent.

TRENDS IN NUTRITION RESEARCH AND TRAINING, 1979-1989

In FY 1988, the NIH led all Federal agencies in financial support of nutrition research and training, with a FY 1988 total of \$276 million, as shown in figure 3. This total represented 72 percent of all Federal expenditures and 92 percent of all DHHS expenditures in nutrition research and training. NIH expenditures have consistently represented between 70 and 73 percent of the total Federal expenditure and between 92 and 95 percent of the total DHHS expenditure in nutrition research and training.

NIH nutrition research and training dollars have steadily increased during the past decade, growing from \$134 million in FY 1979 to \$287 million in FY 1989. NIH actual obligations for nutrition research and training by NIH

Figure 3. Federal Expenditures in Support of Human Nutrition Research and Training, FY 1988



Source: Human Nutrition Research and Information Management (HNRIM) System data base.

Table 1. Actual Obligations, NIH Biomedical Nutrition Research and Training, as a Percentage of Total ICD Obligations, by NIH Component, FY 1989 (in thousands of dollars)

ICD	Nutrition Research and Training*	Total ICD Obligations**	Nutrition as Percentage of Total ICD Obligations
NCI	\$ 64,524	\$1,570,342	4.1
NHLBI	64,287	1,045,508	6.1
NIDR	1,571	130,689	1.2
NIDDK	63,955	559,274	11.4
NINDS	1,095	471,632	<1.0
NIAID	3,797	740,239	<1.0
NIGMS	1,953	682,134	<1.0
NICHD	31,247	425,268	7.3
NEI	6,128	230,999	2.7
NIEHS	10,261	223,309	4.6
NIA	8,494	222,545	3.8
NIAMS	4,128	159,886	2.6
NIDCD	1,174	94,275	1.2
DRR	23,811	381,934	6.2
FIC	92	15,739	<1.0
NCNR	459	29,118	1.6
Total	\$286,975	\$6,982,891 ⁺	4.1

ICD = Institute/Center/Division

* Actual obligations. Source: Human Nutrition Research and Information Management (HNRIM) System data base.

**Obligations. Source: NIH Office of Program Planning and Evaluation.

⁺ Total excludes obligations for Office of the Director, National Library of Medicine, and buildings and facilities.

Table 2. Actual Obligations, NIH Biomedical Nutrition Research and Training, by ICD, FY 1979-1989 (in thousands of dollars)

ICD	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989
NCI	\$ 28,303	\$ 28,687	\$ 30,313	\$ 30,553	\$ 37,336	\$ 50,119	\$ 45,199	\$ 46,223	\$ 52,691	\$ 59,563	\$ 64,524
NHLBI	28,415	32,184	35,213	35,449	38,350	44,553	45,689	49,265	57,285	60,314	64,287
NIDR	1,663	1,648	1,503	1,529	2,072	1,419	1,795	1,211	1,836	1,486	1,571
NIADDK	25,068	26,457	30,906	26,981	33,332	35,969	45,951	—	—	—	—
NIDDK	—	—	—	—	—	—	—	44,697	54,737	60,156	63,955
NINCDS	2,306	2,837	1,559	2,839	2,547	2,652	2,949	2,158	3,367	3,221	—
NINDS	—	—	—	—	—	—	—	—	—	—	1,095
NIAID	1,205	1,047	1,562	1,853	1,606	1,646	1,679	1,830	2,652	3,493	3,797
NIGMS	2,971	2,451	2,503	1,841	2,081	2,271	2,307	2,291	2,710	2,529	1,953
NICHD	20,806	20,410	20,108	18,356	20,164	24,152	26,835	27,662	32,932	34,384	31,247
NEI	3,565	4,166	4,265	5,256	5,571	4,611	5,519	5,176	6,545	6,879	6,128
NIEHS	3,540	3,885	2,106	1,582	1,390	1,768	5,366	4,470	12,880	9,914	10,261
NIA	2,628	4,220	4,133	3,261	4,391	4,757	4,608	5,329	6,934	7,625	8,494
NIAMS	—	—	—	—	—	—	—	2,846	3,424	4,068	4,128
NIDCD	—	—	—	—	—	—	—	—	—	—	1,174
DRR	13,381	11,129	14,330	14,823	15,444	18,874	19,400	19,472	22,089	22,106	23,811
FIC	—	—	—	—	22	127	19	56	57	30	92
NCNR	—	—	—	—	—	—	—	292	472	427	459
Total	\$133,851	\$139,121	\$148,501	\$144,323	\$164,306	\$192,918	\$207,316	\$212,978	\$260,611	\$276,195	\$286,975

component during the past 11 years are shown in table 2. With a few exceptions, the trend in dollars has been steadily upward for all institutes, centers, and divisions.

As shown in table 3, total NIH expenditures for nutrition research and training have increased consistently since FY 1979 and have constituted approximately 4 percent of total NIH obligations during that time. Total NIH biomedical nutrition research and training support is shown in constant, as well as current dollars, in table 3. For example, nutrition research and training support showed a \$153 million increase, or 114 percent, between FY 1979 and FY 1989 in current (unadjusted) dollars. In constant (adjusted) dollars (i.e., adjusted for inflationary price increases), however, nutrition and research training in FY 1989 represented a 12 percent increase over the FY 1979 level.

EXPENDITURES BY HNRIM SYSTEM CATEGORY AND INTEREST AREA

The NIH nutrition research support in the HNRIM System classification categories and the number of grants or contracts funded in each category are shown in table 4. The column labeled "actual obligations" represents the nutrition funding for projects in each classification category, not the funding for the classification category per se. For example, a study of the effects of smoking and diet on coronary heart disease and obesity that was considered to be 60 percent nutrition-related and had a total budget of \$100,000 would contribute \$60,000 towards the actual obligations reported for the area "Cardiovascular Disease and Nutrition" and \$60,000 towards the actual obligations reported for the area "Obesity, Anorexia, and Appetite Control." The column labeled "percent of total"

Table 3. Actual Obligations, NIH Biomedical Nutrition Research and Training, in Current and Constant Dollars and as a Percentage of Total NIH Obligations, FY 1979-1989 (in thousands of dollars)

Fiscal Year	Nutrition Research and Training, Current \$	Nutrition Research and Training, Constant \$*	Total NIH Obligations +	Current Nutrition \$ as a Percentage of Total NIH Obligations
1979	133,851	133,851	3,184,641	4.2
1980	139,121	126,739	3,428,842	4.1
1981	148,501	122,515	3,572,506	4.2
1982	144,323	109,626	3,643,461	4.0
1983	164,306	117,496	4,013,135	4.1
1984	192,918	130,236	4,493,553	4.3
1985	207,316	132,504	5,121,557	4.0
1986	212,978	130,405	5,296,977	4.0
1987	260,611	151,571	6,175,038	4.2
1988	276,195	152,636	6,610,430	4.2
1989	286,975	149,731	7,157,978	4.0

* Based on biomedical R&D price index, FY 1979=100%. Source: NIH Data Book, 1989, NIH Publication No. 90-1261, December 1989.

+ Source: NIH Data Book, 1989. NIH Publication No. 90-1261, December 1989, pp. 8-9.

represents the nutrition funds expended in a given category in relation to total NIH obligations for nutrition research and training, which totaled \$287 million for FY 1989.

As illustrated in the example above, a grant or contract may appear in more than one category. Thus, if all actual obligations in the 41 categories were summed, the sum would exceed the total expenditures of \$287 million.

Although NIH nutrition research encompasses all of the classification categories, the largest component is concentrated in the area of Research in the Biomedical and Behavioral Sciences (codes 1 through 25 and code 35). Codes 51 through 56 represent NIH Special Interest Areas.

SUPPORT BY EXTRAMURAL AND INTRAMURAL CATEGORIES

The NIH supports two broad categories of research: extramural and intramural. The extramural programs are responsible for

roughly 80 percent of the total NIH resources in the form of research grants or contracts.

Through these programs, NIH makes awards of various kinds to institutions throughout the United States and the world. Extramural awards are based on a two-tiered peer review assessment—one for scientific merit and one for program relevance.

Within the NIH itself, and accounting for approximately 13 percent of its budget, is the intramural program. All of the NIH institutes except NIGMS have an intramural component of laboratory and clinical research programs. More than 2,500 research projects are in progress at all times, making the NIH the largest center for biomedical and behavioral research in the world. Boards of scientific counselors are responsible for assessing the quality and direction of the intramural program, and the Office of the Director provides scientific and policy oversight.

The NIH relies on three major funding mechanisms as the administrative instruments

**Table 4. Actual Obligations, NIH Biomedical Nutrition Research and Training,
by HNRIM Classification Category, FY 1989**

Nutrition Research Classification		Number of Grants and Contracts	Actual Obligations* (in thousands of dollars)	Percent of Total**
Code	Area			
1	Maternal Nutrition	152	19,183	7
2	Infant and Child Nutrition	262	36,283	13
3	Adolescent Nutrition	59	9,733	3
4	Adult Nutrition	69	9,635	3
5	Nutrition of the Elderly	106	12,263	4
6	Cardiovascular Disease and Nutrition	440	77,117	27
7	Cancer and Nutrition	513	69,702	24
8	Other Diseases and Nutrition	465	57,191	20
9	Trauma (Burns) and Nutrition	22	1,863	<1
10	Infection, Immunology, and Nutrition	122	17,012	6
11	Obesity, Anorexia, and Appetite Control	304	39,605	14
12	Genetics and Nutrition	165	26,850	9
13	Nutrition and Function	187	28,165	10
14	Nutrient-Nutrient/Drug/Toxicant Interactions	302	34,377	12
15	Other Conditions and Nutrition	526	55,855	19
16	Research on Nutritional Status	139	23,975	8
17	Carbohydrates	140	19,605	7
18	Lipids (Fats and Oils)	414	75,943	26
19	Alcohols	34	4,771	2
20	Proteins and Amino Acids	237	31,996	11
21	Vitamins	405	63,968	22
22	Minerals and Trace Elements	307	47,045	16
23	Water and Electrolytes	127	21,193	7
24	Fiber	21	4,762	2
25	Other Nutrients in Food	49	3,957	1
26	Food Composition	18	2,649	<1
27	Bioavailability	26	3,850	1
28	Effects of Technology on Foods/Diets	7	1,052	<1
29	Other Research in Food Science	5	365	<1
30	Food Consumption Surveys, R&D	20	2,310	<1
31	Research on Dietary Practices, Food Consumption, etc.	146	25,103	9
32	Methods for Educating and Informing the Public	39	13,988	5
33	Other Research in Nutrition Education	9	1,980	<1
34	Effects of Government Policy and Socioeconomic Factors	1	17	<1
35	Parenteral, Enteral, & Elemental Nutrition	60	12,201	4
51	Prevention of Disease	609	67,252	23
52	International Research	28	3,234	1
53	Epidemiological Research	153	18,190	6
54	Education for Professionals	75	5,026	2
55	Education for the Public	44	10,267	4
56	Clinical Trials	155	27,399	10

* The actual obligations represent the *nutrition* funding for projects in each classification area, not the funding for the classification area per se. A grant or contract may be assigned to more than one of these areas. Thus, summing the expenditures by area will yield a value that exceeds the total expenditures and summing the percent of total will yield a value greater than 100 percent.

**The total expenditure of the NIH nutrition program in FY 1989 was \$286,975,000.

for accomplishing its program goals through the efforts of scientists outside the NIH (i.e., extramurally): grants and cooperative agreements (financial assistance awards) and contracts (acquisition awards). Appendix K gives details on NIH award mechanisms. Financial support by NIH of extramural nutrition research and training is provided through all three of these major funding mechanisms. Support of extramural nutrition research utilizes research project grants,

program project grants, center grants, contracts, and cooperative agreements. All of these may include clinical trials; research resources support; reimbursement agreements; research career development awards; and new, academic, and teacher investigator awards. Extramural training in biomedical and behavioral nutrition research is supported through national research service awards, with training grants awarded to institutions and fellowships awarded to individuals. The

Table 5. Actual Obligations, NIH Biomedical Nutrition Research and Training, by Category of Support, FY 1989 (in thousands of dollars)

Funding Mechanism	Item	Breakdown		Total	
		Number	Cost	Number	Cost
Extramural					
Research Grants	Regular	1,437	\$150,697		
	Clinical Trials	126	22,254		
	Total			1,563	\$172,951
Program Projects	Regular	84	28,654		
	Clinical Trials	6	2,106		
	Total			90	30,760
Contracts	Regular	111	16,251		
	Clinical Trials	12	1,770		
	Total			123	18,021
Centers	Regular	49	14,648		
	Clinical Trials	1	124		
	Total			50	14,772
Research Resources Support				305	23,663
Reimbursement Agreements				25	3,510
Career Development Awards				62*	2,480
New Investigator Research Awards				7*	94
Training	Training Grants	47*	2,807		
	Fellowships	27*	416		
	Total			74*	3,223
Subtotal, Extramural					269,474
Intramural					
Projects				115	17,501
Training				3*	**
Subtotal, Intramural					17,501
Total NIH Biomedical Nutrition Research and Training					\$286,975

* Number of training grants.

**Information not provided.

intramural nutrition program consists of research projects and training.

The NIH FY 1989 actual obligations in biomedical nutrition research and training are shown by category of support in table 5. Of the \$287 million expended by NIH on nutrition research and training in FY 1989, 94 percent supported extramural projects. The percentage of support for extramural projects is much higher for NIH nutrition research funding than for total NIH research funding. Research grants comprised the largest category, with 1,563 projects supported at an expenditure of \$173 million; of these, 126 projects, with an expenditure of \$22 million, were clinical trials. Program projects formed the next largest category, with 90 projects (6 clinical trials) at a cost of \$31 million (\$2 million for clinical trials). Research resources support was the third largest category, at 305 projects and \$24 million.

NUTRITION RESEARCH TRAINING

The NIH supports training in biomedical and behavioral nutrition research in both the extramural and the intramural programs. Within the extramural program, two basic mechanisms are used for nutrition training support: institutional awards and individual awards (see appendix K). The institutional awards, commonly called "training grants," are designed to enable institutions to make training awards to individuals selected by them for predoctoral and postdoctoral research training. In FY 1989, NIH spent \$2.8 million on 47 training grants in nutrition. The postdoctoral individual national research service awards, called "fellowships," are awarded to provide postdoctoral research training to individuals to broaden their scientific background and extend their potential for research. In FY 1989, \$416,000 was expended for 27 fellowships in nutrition.

Appendices



Legislative Base for Nutrition at the NIH

On November 20, 1985, the Health Research Extension Act of 1985 became Public Law 99-158. This act amended the Public Health Service Act "...to revise and extend the authorities under that Act relating to the National Institutes of Health and for other purposes."

Four institutes—the National Cancer Institute (NCI); National Heart, Lung, and Blood Institute (NHLBI); National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); and National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)—have specific mandates to conduct nutrition research at the NIH. These mandates are as follows:

NCI. Section 413(a)--"establish an information and education center to collect, identify, analyze, and disseminate on a timely basis, through publications and other appropriate means, to cancer patients and their families, physicians and other health professionals, and the general public, information on cancer research, diagnosis, prevention, and treatment (including information respecting nutrition programs for cancer patients and the relationship between nutrition and cancer)...."

NHLBI. Section 420--"(1)...dissemination of information regarding diet and nutrition, environmental pollutants, exercise, stress, hypertension, cigarette smoking, weight control, and other factors affecting the prevention of arteriosclerosis and other cardiovascular diseases and of pulmonary and blood diseases; and (2) the dissemination of information designed to encourage children to adopt healthful habits respecting the risk factors related to the prevention of such diseases...."

Section 421(a)(1)(A)--"investigation into the epidemiology, etiology, and prevention of all forms and aspects of heart, blood vessel, lung, and blood diseases, including investigations into the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences involved in the epidemiology, etiology, and prevention of such diseases...."

NIDDK. Section 426--"conduct and support of research, training, health information dissemination, and other programs with respect to diabetes mellitus and endocrine and metabolic diseases, digestive diseases and nutritional disorders, and kidney, urologic, and hematologic diseases...."

Section 428--"(a)(1) In the Institute there shall be a Division Director for Diabetes, Endocrinology, and Metabolic Diseases, a Division Director for Digestive Diseases and Nutrition...responsible for—A) developing a coordinated plan (including recommendations for expenditures) for each of the national research institutes within the National Institutes of Health with respect to research and training concerning diabetes, endocrine and metabolic diseases, digestive diseases and nutrition, and kidney, urologic, and hematologic diseases; (B) assessing the adequacy of management approaches for the activities within such institutes concerning such diseases and nutrition and developing improved approaches if needed; (C) monitoring and reviewing expenditures by such institutes concerning such diseases and nutrition; and (D) identifying research opportunities concerning such diseases and nutrition and recommending ways to utilize such opportunities...(b)(1) carry out programs of support for research and training (other than training for which National Research Service Awards may be made under section 487) in the diagnosis, prevention, and treatment of diabetes mellitus and endocrine and metabolic diseases, digestive diseases and nutritional disorders, and...(2) establish programs of evaluation, planning, and dissemination of knowledge related to such research and training."

Section 432--"There are established within the advisory council for the Institute appointed under section 406 a subcommittee on diabetes and endocrine and metabolic diseases, a subcommittee on kidney, urologic, and hematologic diseases....The subcommittees are authorized to review applications made to the Director of the Institute for grants for research and training projects relating to the diagnosis, prevention, and treatment of the diseases for which the subcommittees are established and shall recommend to the advisory

council those applications and contracts that the subcommittees determine will best carry out the purposes of the Institute. The subcommittees shall also review and evaluate the diabetes and endocrine and metabolic diseases, digestive diseases and nutrition, and kidney, urologic, and hematologic diseases programs of the Institute and recommend to the advisory council such changes in the administration of such programs as the subcommittees determine are necessary."

NIAMS. Section 440(6)--"...projects for investigation into the epidemiology of all forms and aspects of arthritis and musculoskeletal diseases, including investigations into the social, environmental, behavioral, nutritional, and genetic determinants and influences involved in the epidemiology of arthritis and musculoskeletal diseases...."

Other institutes that conduct and support nutrition research do so under much broader authority. Each conducts research programs in the "diagnosis, prevention, and treatment" of specific diseases and life processes within their areas of responsibility. These authorities are as follows:

- National Institute of Dental Research (NIDR): Section 453
- National Institute of Neurological Disorders and Stroke (NINDS): Section 457
- National Institute of Allergy and Infectious Diseases (NIAID): Section 446
- National Institute of General Medical Sciences (NIGMS): Section 461
- National Institute of Child Health and Human Development (NICHD): Section 448
- National Eye Institute (NEI): Section 445
- National Institute of Environmental Health Sciences (NIEHS): Section 463
- National Institute on Aging (NIA): Section 443
- National Center for Research Resources (NCRR): Section 479
- National Institute on Deafness and Other Communication Disorders (NIDCD): Section 464
- Fogarty International Center (FIC): International Cooperation Authority, Section 482
- National Center for Nursing Research (NCNR): Section 483
- Training Authority: Section 487

To facilitate and enhance the distribution of information regarding these specific disease areas to health professionals, patients, and the public the following ICDs have established clearinghouses: NIDDK (Section 427) has established two clearinghouses, the National Digestive Diseases and Nutrition Clearinghouse and the National Kidney and Urologic Diseases Information Clearinghouse; NIAMS (Section 438 (b) has established the National Arthritis and Musculoskeletal and Skin Diseases Clearinghouse; the NIA (Section 4435E) Alzheimer's Disease Education and Referral (ADEAR) Center; and the NIDCD (Section 464B) National Deafness and Other Communication Disorders Information Clearinghouse. Nutrition information often is included.

In order to place more emphasis on research on health maintenance and disease prevention, the Health Research Extension Act of 1985 established the appointment of an Associate Director for Disease Prevention within the NIH Office of the Director (402(f)), NCI (416), and NICHD (451). A similar position exists at NHLBI (423) by current law. The associate directors are to "assure that each Institute's research plans include sections dealing with such prevention-related research as investigations into the epidemiology of disease; studies of the etiology of diseases (including the effect of diet and other personal habits on the development of disease, and the effect of environmental factors, including air, water, radiation, and toxic substances, on the development of disease); research into immunizations against disease; studies of the means to preclude the development of disease through changes in personal habits and environmental factors; and studies of methods for, and the cost-effectiveness of, population screening programs." In 1986, NIH established the Office of Disease Prevention (ODP) within the Office of the Director, under the purview of the NIH Associate Director for Disease Prevention. The Associate Director for Disease Prevention is responsible for promoting and coordinating the research programs of all Institutes regarding the prevention of disease.

Members of the NIH Nutrition Coordinating Committee⁺

Chairperson: Darla E. Danford, M.P.H., D.Sc., R.D.
DNRC

ICD*	Member/Alternate
NCI	Peter Greenwald, M.D. <i>Ritva Butrum, Ph.D.</i>
NHLBI	Nancy Ernst, M.S., R.D. <i>Barbara H. Dennis, Ph.D.</i>
NIDR	Joseph E. Ciardi, Ph.D.
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⁺As of September 1, 1989

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As of September 1, 1989

Members of the Nutrition Education Subcommittee⁺

Chairperson and Executive Secretary: Karen Donato, M.S., R.D.
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OC	Don Ralbovsky

⁺ As of September 1, 1989

Program Announcements, Requests for Applications, and Requests for Proposals in Nutrition, FY 1989

A major responsibility of the DNRC and its NCC is to identify areas for further research and bring them to the attention of the institutes for the development and publication of program announcements (PAs), requests for applications (RFAs), and requests for proposals (RFPs). When areas of nutrition research are of interest to more than one institute, including those of Alcohol, Drug Abuse, and Mental Health Administration, joint PAs often are developed under the auspices of the NCC.

- A PA is a formal statement of an NIH extramural research activity or of the initiation of a new or modified mechanism of support. It may describe new or modified program interests or simply be a reminder of continuing interest.
- An RFA is a formal statement that invites grant applications in a well-defined scientific area to accomplish specific program purposes, generally identifies only one application receipt date, and indicates whether or not funds have been set aside for the competition and, if so, the amount of funds and/or the expected number of awards to be made. An RFA may be reissued as necessary.
- An RFP is the government's invitation to prospective offerors to submit a contract proposal based on the terms and conditions set forth in the RFP by the statement of work that describes the nature of intended procurement. The number of contracts awarded as a result of an RFP is smaller than the number of applications funded as a result of PAs and RFAs.

PAs, RFAs, and RFPs in nutrition research and training published in the "NIH Guide for Grants and Contracts" in FY 1989 follow in chronological order.

<i>Issued by</i>	<i>Date</i>	<i>Type</i>	<i>Title</i>
NIAAA	10/88	RFA	Research Grants on Alcohol and Immunology Including Acquired Immunodeficiency Syndrome
NIDDK	10/88	RFA	Digestive Diseases Core Center
NICHD	10/88	RFA	Nutritional Therapy of Inborn Errors of Metabolism
NIAID	10/88	RFA	Centers for AIDS Research
NHLBI	10/88	RFA	Specialized Centers of Research (SCOR) in Hypertension
NIDDK	11/88	RFA	Small Grants for Researchers in Digestive Diseases and/or Nutrition
NICHD	11/88	PA	Research Program on Breastfeeding and Human Milk
NHLBI	12/88	RFA	Models for Treating High Blood Cholesterol
NHLBI	12/88	RFA	Cellular and Molecular Interactions of Lipoproteins and the Hemostatic System in Atherosclerosis and Thrombosis
NCI	12/88	RFA	Worksite Health Promotion Intervention

NCI	1/89	RFA	Relationship Between Blood and Tissue Micronutrient Levels in Humans
NIDDK NIA	1/89	RFA	Core Grants for Clinical Nutrition Research Units (CNRUs)
NHLBI	2/89	RFA	HMG CoA Reductase Inhibitors in the Elderly: Pilot Study
NCI	2/89	RFA	Cancer Prevention and Control Research Small Grants Program
NICHHD	3/89	RFA	Mental Retardation Research Centers
NIDDK	3/89	RFA	Research Training and Career Development Awards for Physicians in Nutrition
NCI	3/89	RFA	Avoidable Mortality from Cancer in Native American Populations
NCI	3/89	RFA	Primary Prevention: Smoking/Smokeless Tobacco Use and Dietary Change in Native American Populations
NIA NCNR	3/89	RFA	Reducing Frailty and Injuries in Older Persons
NIDDK NIA NIAID NICHHD NIDR NIEHS NEI NHLBI NIMH NINDS NCNR	3/89	PA	Studies of Diabetes Mellitus and Related Problems
NEI	3/89	RFP	Age Related Eye Disease Study
NIA NIDDK	5/89	PA	Etiology and Impact of Atrophic Gastritis and Hypochlorhydria in Advancing Age
NCI	6/89	RFA	Minority-Based Community Clinical Oncology Program
NIDDK	6/89	RFA	Diabetes Centers
NHLBI	8/89	PA	Social Support and Cardiovascular Disease
NIA	8/89	RFA	Pharmacology in Geriatric Medicine
NIDDK	8/89	PA	Small Grants to Facilitate Use of New Techniques by Researchers in Diabetes, Endocrinology and Metabolism
NCI	8/89	RFA	Data-Based Intervention Research for Public Health Agencies

NIDDK	9/89	PA	Cholesterol Nucleation in Human Gallbladder Stone Disease
NHLBI	9/89	RFA	Postprandial Lipoproteins and Atherosclerosis
NCI	9/89	RFP	Clinical Evaluation of Fruit and Vegetable Based Experimental Food Supplements
NIDR	9/89	PA	The Effects of Oral Factors on Taste and Smell
NCI	9/89	RFA	Mechanisms of Protease Inhibitor Anticarcinogenesis
NCI	9/89	RFP	Methods Development for Phytochemical Compliance Markers in Designer Foods
NCI	9/89	RFA	Prevention Clinical Trials Utilizing Intermediate Endpoints and their Modulation by Chemopreventive Agents
NIDCD	9/89	PA	Nasal Chemoreception: Regeneration and Trophic Interactions

NIH Guide Notices

NIH ADAMHA	1/89	Notice	Inclusion of Minorities in Study Populations
DNRC	8/89	Notice	Availability of Fish Oil Test Materials

NCC-Sponsored Conferences and Workshops, FY 1989

NIA, NIDDK	Conference on Assessment of Nutritional Status in the Elderly October 19-21, 1988
NHLBI	First National Cholesterol Conference November 9-11, 1988
NIDDK, NHLBI	Seminar on Impact of Lipids on the Progression of Renal Disease November 10, 1988
NICHD	Fourth International Meeting on Human Nutrition: Breastfeeding, Infection, and Infant Growth and Development in Emerging Countries November 16-19, 1988
NIA, NIDDK	Symposium on Overview and Recommendations from the 1988 NIA/NIDDK Conferences on Nutrition and Aging at Gerontological Society of America November 18-22, 1988
NCI	Second International Conference on Mechanisms of Antimutagenesis and Anticarcinogenesis December 4-9, 1988
ICHNR, DNRC	Fourth Biennial Conference for Federally Supported Human Nutrition Research Units and Centers February 15-16, 1989
NCI	Annual Meeting of the American Society of Preventive Oncology March 20-21, 1989
NIDDK	The Gordon Conference on Lipid Metabolism June 26-30, 1989
NCI	N-Nitroso Compounds (NOC), Mycotoxins and Tobacco Smoke: Relevance to Human Cancer July 2-7, 1989
NIDDK	FASEB Summer Research Conference on Micronutrients: Trace Elements July 23-28, 1989
NCI, NIDDK	FASEB Summer Research Conference on Nutrients and Gene Expression in Carcinogenesis July 30-August 4, 1989
NIDDK, NICHD	FASEB Summer Research Conference on Regulation of Energy Balance and Nutrient Partitioning July 30-August 4, 1989

NIDDK, NICHD, DNRC	14th International Congress of Nutrition August 20-25, 1989
NIDDK, NCI, NHLBI, NICHD, NIA, DNRC	Workshop on Basic and Clinical Aspects of Regional Fat Distribution September 11-13, 1989
NIDR, NIA, DNRC	Workshop on Diet and Nutrition and the Maintenance of Oral Health in the Elderly September 21, 1989
NINDS, DNRC	Workshop on Diet and the Nervous System September 28, 1989

Abstracts from NCC-Sponsored Scientific Seminars, FY 1989

Dietary Habits of Athletes

Patricia A Deuster, Ph.D., Director of Human Performance Laboratory, Department of Military Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD (October 13, 1988)

Training to become a U.S. Navy Sea, Air, and Land (SEAL) team member is extremely rigorous and demanding. Attrition is high during the first six weeks when physical endurance is emphasized, with an attrition rate of up to 80 percent reported. To evaluate whether nutritional issues might contribute to attrition, a dietary survey was conducted on 277 SEAL trainees. The major objectives were to determine 1) energy intakes and the distribution of energy-providing nutrients; 2) intakes of selected minerals relative to the Recommended Dietary Allowances (RDA); and 3) how nutrient intakes by SEAL trainees compared to a population of similar activity patterns; male triathletes (n=50) were studied for comparison. Energy intake by SEAL trainees was 3886 ± 78 kcal/day, and the percent of energy derived from carbohydrates was 43 percent. This percent was lower than the triathletes (53 percent) and lower than usual recommendations for endurance athletes (58 percent). Intakes of fat, protein, cholesterol and sodium by trainees (177 g, 151 g, 1009 mg, and 5993 mg/day, respectively) were high relative to the RDA and Dietary Goals, whereas intakes by triathletes conformed with recommendations (92 g, 102 g, 308 mg, and 3937 mg/day, respectively). Although mean intakes of calcium, magnesium, iron, zinc, and copper by SEAL trainees exceeded the RDA, over 30 percent were consuming below the RDA; patterns of mineral intake by the triathletes were similar. In sum, although no specific nutritional issues related to attrition were noted, nutrition education would be of value to these young men. The diets of SEAL trainees would clearly not be advocated for maintenance of good health, whereas the triathletes' diets reflected current dietary goals. The precise impact of dietary habits on physical performance remains to be determined.

Nutrition Education for Adults

Betty Alford, Ph.D., R.D., Extramural Associate and Professor in Nutrition, Department of Nutrition and Food Sciences, Texas Woman's University, Denton, TX (November 3, 1988)

For adult nutrition education the audience comes with past experiences and beliefs that may conflict with our message. Effort to interest the adult learner is required early to continue participation. For clear education there must be definition of terms. Nutrition education is the transmission of knowledge to the public about their nutritional needs and about the nutritive value of foods to motivate them to transform this knowledge into eating behavior which promotes health and well being (JADA 1978). The use of learning theories helps to avoid personal bias. The major families of contemporary learning theories are the Behavioristic family of stimulus-response conditioning and the Gestaltfield family of cognitive theories (Bigge, ML, Learning Theories for Teachers, Harper & Row, 1982).

In a study based on a holistic education theory with missionaries the results showed that increased knowledge improved attitude toward the importance of nutrition. The study of Schwartz (JADA 1975) supports this, while the study of Roseander and Sims (J Nutr Ed 1981) does not.

Scientific manpower studies point to the problem in nutrition education. Over half the adult population does not have enough science background to understand nutrition. There is great need to translate research findings into simple terms so that people can adopt healthy behaviors.

Some guidelines for developing information for low literate and semi-literate populations are provided in a brief article in J Nutr Ed (Oct.1988). Some examples follow: Provide opportunities for people to learn by seeing and hearing. Use foods in presentations. Use large print. Keep illustrations simple. Arrange the page

from left to right. Be direct. Remember that effective commercials teach with few words and create images. The message of nutrition education is complex. Work to make it simple for the learner.

Recent Advances in Nutrition and Aging Research

Jeffrey Blumberg, Ph.D., F.A.C.N., Assistant Director and Professor of Nutrition, USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA (December 1, 1988)

Persons 65 years and older comprise 12 percent of the U.S. population, and those over 75 represent its fastest growing segment. Nutrition problems of this group have come to national attention for several reasons. Nutritional status surveys of the elderly have shown a low-to-moderate prevalence of frank nutrient deficiencies or an increased risk of deficiencies in institutionalized and non-institutionalized groups. Nutritional status appears to influence the age-related rate of functional decline in a wide variety of organ systems. Nutrition also may be an important factor in progressive changes in body composition associated with aging, such as the loss of lean body mass and bone and the increase in adipose tissue. Evidence demonstrates nutrition is linked to many chronic diseases afflicting older adults and the elderly.

There is now increased interest in diet and nutrition as a vital component of the health care delivery system for the healthy elderly. The need to assist those requiring specific dietary management through the health care delivery system and to identify non-institutionalized population groups vulnerable to nutritional deficiencies is becoming critical.

The current Recommended Dietary Allowance (RDA) provides guidelines for assessing the intake of energy and specified nutrients for adults up to age 50 and for 51 years and above. However, essentially all studies on nutrient requirements have been carried out on young adults and the estimated allowances for older adults and the elderly are largely based on extrapolation. The current RDA provides for a downward adjustment in energy (calorie) allowance with age but protein and most micronutrients are not so adjusted and are maintained at middle-age adult levels. Although this situation has been imposed by inadequate data, it represents a lack of realism to assume that a 51 year old and 91 year old have similar requirements. This is a period of dynamic change in which nutrient and energy requirements between individuals and between population subgroups become greatly increased.

Among the factors contributing to changes in food choices and increased variability in nutrient absorption, metabolism and utilization are: a) social circumstances, including isolation and physical activity levels; b) differences in severity and rates of decline of body functions, particularly of the gastrointestinal tract and senses of smell and taste; c) presence of chronic, degenerative diseases; and d) drug- and alcohol-induced nutrient deficiencies.

Low dietary intakes account for much of the poor vitamin and mineral nutriture reported among various elderly groups. Despite many problems in assessing their nutritional status, including absence of adequate age-adjusted anthropometric, biochemical and clinical standards, it appears the 1980 RDA for many nutrients are appropriate to apply to the healthy elderly. However, vitamin and mineral nutriture of the elderly is a subject of ongoing investigation and evolving knowledge. What is considered fact today will likely become modified or challenged in the years to come, particularly as linkages between specified nutrients and chronic disease patterns emerge. Some data indicate that the 1980 RDA for vitamin A and folate may be too high for the elderly population from the point of view of preventing deficiencies. The RDA for vitamins D, B₆, and B₁₂ might be too low, at least for certain groups of elderly. Data as to the appropriateness of the RDA for vitamin E are conflicting, but the present RDA seems adequate for thiamin, riboflavin, and ascorbic acid. There is almost a total lack of data vis-a-vis the appropriateness of the 1980 safe and adequate intake recommendations for vitamin K, niacin, biotin, and pantothenic acid. The RDA for calcium has been demonstrated to be lower than necessary to maintain a zero metabolic balance in older adults. Little is known concerning age

effects on trace mineral metabolism. However, marginal zinc and chromium deficiencies may be related to certain signs and symptoms associated with old age. Data are now becoming available which suggest the criteria used to establish the current RDA may be inappropriate to aging concerns and/or lack the sensitivity to detect subtle biochemical alterations with significant consequences for the aging process.

Decreasing energy intake with advancing age has important implications for the diet in terms of protein, vitamins and minerals. Allowances for these nutrients currently assume levels of overall energy intake considerably exceeding the amounts of foods the elderly actually consume. Dietary quality becomes difficult to assure when overall energy intake is low and requires a careful selection of nutrient-dense foods. Energy intake decreases more rapidly in the very old due to the disabilities that limit physical activity.

Although evidence is accumulating that some nutrient requirements may be altered for the elderly, many are already resorting to self-prescribed vitamin and mineral supplement use. However, despite the 30-70 percent prevalence of nutrient supplementation among the elderly, the selection of such supplements often appears irrational and inappropriate to real needs.

A multitude of non-nutritional factors, including genetics, physical activity, and medications, can influence dietary intakes and nutrient utilization and jeopardize beneficial effects of essential nutrients on health. Today, the concept is evolving that nutritional requirements for the elderly should be adjusted to observed age-associated changes in body composition and physiologic function. Contributions from current research efforts in nutrition and aging should allow for the determination of optimal body composition and levels of function for the determination of optimal body composition and levels of function for different age groups so that nutrient intakes may be designed to achieve these criteria and also reduce the risk of developing age-dependent diseases and disorders. This knowledge is critically important as it has already been established that many of the diseases common among the elderly, e.g., heart disease, diabetes, atherosclerosis, hypertension, and cataract, possess strong etiological links to nutrition.

Vitamin C: Concentration Dependent Function in Situ

Mark A. Levine, M.D., Senior Investigator, Laboratory of Cell Biology and Genetics, NIDDK/NIH, Bethesda, MD
(January 5, 1989)

I. Ascorbic acid was found to regulate biosynthesis *in situ* of the stress hormone norepinephrine from the substrate dopamine, in isolated adrenal medullary chromaffin cells and chromaffin granules. The mechanism of action of ascorbic acid *in situ* was found to be much more complex than for the isolated enzyme dopamine beta-monooxygenase. These data provide strong support for the essential role of *in situ* enzyme kinetics in determining optimal vitamin requirements.

II. Ascorbic acid requirements for norepinephrine biosynthesis were investigated in intact bovine chromaffin granules, using the physiologic substrate dopamine and a novel coulometric electrochemical detection HPLC system for ascorbic acid. Ten mM external dopamine, 1 mM Mg-ATP, and 1 mM ascorbic acid produced maximal norepinephrine biosynthesis without granule lysis. When external ascorbic acid was omitted, intragranular ascorbic acid was consumed in a 1:1 ratio with respect to norepinephrine biosynthesis. The initial concentration of intragranular ascorbic acid was 10.5 mM, which was depleted in stepwise fashion to 15 lower concentrations, over the range of 9.2 mM to 0.2mM. Chromaffin granules containing these varying concentrations of intragranular ascorbic acid were then incubated with 1 mM exogenous ascorbic acid, and norepinephrine biosynthesis from dopamine was determined. The apparent K_m of norepinephrine biosynthesis for intragranular ascorbic acid was 0.57 mM by Eadie-Hofstee analysis and 0.68 mM by Lineweaver-Burk analysis. These data indicate that intragranular ascorbic acid is available and required for norepinephrine

biosynthesis, that ascorbic acid is a true cosubstrate for dopamine beta-monooxygenase, and that intragranular ascorbic acid is maintained by extragranular ascorbic acid. Continued norepinephrine biosynthesis in granules is dependent on both intragranular and extragranular concentrations of the vitamin. Furthermore, *in situ* kinetics of dopamine beta-monooxygenase for ascorbic acid may be most accurately determined using intact granules and the true physiologic substrate.

III. A method for the detection of ascorbic acid using high performance liquid chromatography with coulometric electrochemical detection and a technique for stabilization of the vitamin are described. Since less than pmole of ascorbic acid can be detected, this assay provides significantly greater sensitivity than any of the currently available procedures. Stabilization of 10 pmoles or less of ascorbic acid at room temperature for up to 4 hours and for several weeks at -70°C facilitates storage of a large number of samples and measurement of ascorbic acid using an automated sampling device. This method was used to quantitate the amounts of ascorbic acid in human polymorphonuclear leukocytes and bovine adrenomedullary chromaffin granules. The calculated concentrations found for human neutrophils (1.35 mM) and bovine chromaffin granules (9.25 mM) are in agreement with previously published data. The assay is suitable for the determination of ascorbic acid in biological samples where only a small amount of tissue is available or very low amounts of ascorbic acid are found. This method is the first application of coulometric electrochemical detection to ascorbic acid HPLC analysis.

IV. The transport, accumulation, and distribution of ascorbic acid were investigated in isolated human neutrophils utilizing a new ascorbic acid assay, which combined the techniques of high performance liquid chromatography and coulometric electrochemical detection. Freshly isolated human neutrophils contained 1.0-1.4 mM ascorbic acid, which was localized ≥ 94 percent to the cytosol, was not protein bound, and was present only as ascorbic acid and not as dehydroascorbic acid. Upon addition of ascorbic acid to the extracellular medium in physiologic amounts, ascorbic acid was accumulated in neutrophils in millimolar concentrations. Accumulation was mediated by a high affinity and a low affinity transporter; both transporters were responsible for maintenance of concentration gradients as large as fifty-fold. The high affinity transporter had an apparent K_m of 2-5 μM by Lineweaver-Burk and Eadie-Hofstee analyses, and the low affinity transporter had an apparent K_m of 6-7 mM by similar analyses. Each transporter was saturable and temperature dependent. In normal human blood the high affinity transporter should be saturated, while the low affinity transporter should be in its linear phase of uptake. These findings may have important implications regarding ascorbic acid function in human neutrophils, and human ascorbic acid requirements.

V. Ascorbic acid (vitamin C) was found in isolated human mononuclear leukocytes and their purified components in millimolar concentration. Intracellular ascorbic acid was depleted ≥ 96 percent during cell culture and was rapidly reaccumulated after addition of physiologic concentrations of ascorbic acid to the extracellular medium. Purified cells maintained concentration gradients of ascorbic acid as large as 100-fold across the plasma membrane. The ability to vary intracellular ascorbic acid concentrations over such a wide range makes it possible for the first time in these cells to study ascorbic acid function in direct relationship to intracellular concentration.

Genetic and Environmental Influences on Body Composition, Energy Balance, and Altered Metabolism Associated with the Development of Obesity

Claude Bouchard, Ph.D., Department of Physical Activity Science Laboratory, Laval University, Quebec, Canada (February 2, 1989)

Three different lines of evidence will be used to demonstrate the role of the genotype in human variation for total body fat, and particularly abdominal fat. First, based on data obtained in about 1700 individuals from 9 different kinds of relatives by descent or by adoption, and using the analytical methods from the field of

genetic epidemiology, we concluded that the additive genetic effect was quite low (less than 10 percent) for subcutaneous fat but reached about 25 percent to 30 percent of the age and gender adjusted fat mass, percent fat and regional fat distribution. We could not find any evidence for a larger maternal or paternal effect, a specific X- or Y-linked effect, or a sex-limited effect. From data obtained in pairs of parent/child, dizygotic (DZ) and monozygotic (MZ) twins, we also reported that the heritability for resting metabolic rate, thermic response to a standardized meal and energy cost of submaximal exercise was significant and reached at least 40 percent of the variance after adjustment for the proper concomitants. Second, using an experimental genetic strategy, we were able to conclude that the genotype was an important determinant of the human adaptive response to chronic overfeeding, in both short-term (22 days) and long-term (100 days) studies. In the latter case, 12 pairs of young adult male MZ twins were overfed by a total of 84,000 kcal over 100 days. We found 3 times more variance between pairs than within pairs in the changes observed in subcutaneous fat, total fat mass and body energy gain as well as for the various components of energy expenditure. However, the genotype-environment interaction effect was much stronger (F ratio ≥ 6) for the changes in visceral fat deposition. Third, we have undertaken the search for genetic markers of the obese state and of the sensitivity to chronic overfeeding. Thus far, we have identified 10 proteins of the adipose tissue from 2-D gel electrophoresis which exhibit genetic variation. Two of these are particularly interesting: variants for the 8D2 protein being primarily observed in the MZ twins gaining less fat with overfeeding, while 10DE variants were seen in the high gainers. These studies have been extended to nuclear and mitochondrial DNA using RFLP technology. One interesting observation is that obese women exhibit more mtDNA polymorphism than lean controls.

Nutrition Activities in the Centers for Disease Control

Frederick Trowbridge, M.D., Director, Division of Nutrition; Mary Serdula, M.D., Medical Epidemiologist; David Williamson, Ph.D., Nutrition Epidemiologist, Centers for Disease Control, Atlanta, GA (June 1, 1989)

In October 1988, the U.S. Department of Health and Human Services approved the creation of the Center for Chronic Disease Prevention and Health Promotion (CCDPHP) at the Centers for Disease Control (CDC). The new center was established in the belief that more emphasis was needed on chronic disease prevention if CDC was to accomplish its mission of preventing unnecessary illness, disability, and death. To meet the challenge, CCDPHP stresses translating research findings into effective community-based programs, strengthening the delivery of preventive health services, and designing programs to meet the needs of minority groups.

The formation of the center was the culmination of 3 years of study and planning. The first challenge was to define the scope of CDC's involvement in preventing chronic disease—an area that encompasses a wide variety of ailments and that cannot be crisply delineated. CDC's internal Chronic Disease Advisory Committee, which was formed to study the agency's role, began with the broad definition of chronic disease as those illnesses that are prolonged, do not resolve spontaneously, and are rarely cured completely. The committee used two principal criteria to determine which of the many diseases that fit this definition should be targeted by CDC. These criteria were that the illnesses be preventable and that they pose a significant burden in mortality, morbidity, and cost.

The committee identified the 10 preventable chronic diseases that take the greatest toll in American lives and quality of life: coronary heart disease, chronic obstructive lung disease, cerebrovascular disease, diabetes, lung cancer, cirrhosis/alcoholism, breast cancer, colorectal cancer, chronic musculoskeletal disease (including arthritis, osteoporosis, and low back pain), and cervical cancer. The major risk factors associated with many of these diseases, as well as those associated with pregnancy—smoking, poor nutrition, sedentary lifestyle, occupational exposure, alcohol misuse, and inadequate preventive health services—can be altered through intervention.

To deliver a full prevention and control program in all of these areas, the center uses an integrated approach that combines programs focusing on the specific diseases with programs focusing on risk factors. This approach allows CCDPHP to address the full breadth and depth of these complex health issues. The strength of the center's efforts lies in combining this approach with the goal of transferring technology and information to the state and local health departments for use in implementing community interventions that can directly influence the incidence of chronic disease.

The new center brought together several existing CDC units and added some that are new or modified. The Office on Smoking and Health continues to coordinate all Department of Health and Human Services activities related to smoking and health, including the Surgeon General's report. The Division of Reproductive Health promotes infant, maternal, and child health; family planning; and contraceptive safety. The Division of Nutrition works to improve the nutritional status of low-income, high-risk, minority populations in the United States and to reduce nutritionally related risk factors. The new Division of Adolescent and School Health, which particularly addresses AIDS education in the public schools, is concerned with the prevention of primary health risks among youth. The Division of Chronic Disease Control and Community Intervention, which combined the Division of Health Education and components of the Division of Chronic Disease Control, is developing prevention and control programs aimed at cancer, cardiovascular disease, and a variety of modifiable risk factors. The Division of Diabetes Translation (changed from the Division of Diabetes Control to reflect a new congressional mandate originally recommended by the National Diabetes Advisory Board) will work to translate into actual patient care the scientific advances made through diabetes research. The long-term goal of the newly organized Office of Surveillance and Analysis is to establish a nationwide state-based surveillance system for chronic diseases and their related risk factors.

As an essential part of meeting its commitment to preventing and controlling chronic disease, CCDPHP engages in a number of surveillance programs and in epidemiologic, laboratory, and behavioral studies. One of the center's principal epidemiologic tools is the Behavioral Risk Factor Surveillance System, a state-based system for monitoring adverse health behaviors associated with chronic disease among adults. The flexibility of the system allows states to add questions to the survey as health emergencies arise. Consequently, when AIDS became a public health concern, states were able to quickly assess related knowledge, attitudes, and behaviors and to target health education needs.

Other studies address a variety of chronic disease and health promotion issues. Efforts are currently under way to use existing health data sets, such as hospital discharge records and disease registries, to define national trends in the incidence and prevalence of chronic disease. This information will be used to assess the impact of specific diseases and to evaluate the success of intervention and prevention programs. To more effectively encourage regular exercise, epidemiologists and behavioral scientists are working together to study both the effects of physical activity on health and the factors that motivate people to exercise. In the area of school health education, the center is studying the knowledge, attitudes, and behaviors of youth about AIDS and other health issues. Awareness of these characteristics is essential in planning interventions in the public schools. At the request of state health departments, the center also investigates unexplained clusters of chronic disease.

A number of programs are under way to combat specific chronic diseases. The center works with state health departments on breast cancer control projects that promote screening mammography, advanced training for technicians, equipment testing, and peer review to assure quality control in mammography. Cooperative epidemiologic studies to discover the barriers to preventing cervical cancer are in progress. The center has also worked with states and voluntary agencies to develop proficiency testing for cytology laboratories reviewing Pap smears. The center coordinates the production of a guide for primary care practitioners in the prevention and treatment of complications of diabetes and has been instrumental in getting insurers to cover the cost of diabetes education.

The center is extensively involved in the area of maternal and child health. The National Maternal Mortality Surveillance System is maintained as an avenue for reporting pregnancy-related deaths in the United States. All reported deaths are investigated, and liaison has been established with local and national organizations of

obstetricians and gynecologists to improve obstetric practices. The center assists states in their epidemiologic studies of the dynamics of infant mortality, teenage pregnancy, and smoking cessation during pregnancy and has helped several states develop smoking cessation programs for women attending public health clinics. Three voluntary, state-based systems--the Pregnancy Nutrition Surveillance System, the Pediatric Nutrition Surveillance System, and the Pregnancy Risk Assessment Monitoring System--monitor nutrition-related problems and behavioral risk factors among high-risk pregnant women and their children. The center also participates in several ongoing studies of the safety and efficacy of available contraceptive methods, including tubal sterilization, oral contraceptives, and intrauterine devices. Staff are also involved in helping developing countries improve maternal health status, pregnancy outcome, and child survival, especially through child spacing and improved nutrition.

To reach individuals in localities where specific risk factors are most prevalent, the center operates the Planned Approach to Community Health (PATCH) Program. CCDPHP staff work with state and local health departments and community members to organize local intervention programs. The center provides materials and technical assistance, and the communities invest their time and resources and make the programs work. Programs have focused on cholesterol screening and nutrition, smoking cessation, seat-belt use, alcohol misuse, and prevention of injuries from falls. The PATCH program conducts international training conferences, and other countries are beginning to use the PATCH process. Additional efforts to encourage quality interventions at the local level include the Secretary's Community Health Promotion Award Program, which is coordinated by CCDPHP and is designed to recognize exceptional health promotion interventions throughout the country.

The Preventive Health and Health Services Block Grant helps fund state's efforts to combat chronic diseases and to offer health education. States may use these funds for detection and treatment programs for hypertension and elevated serum cholesterol, for programs designed to reduce the incidence of chronic diseases, for immunization services, and for programs targeted at screening and managing uterine and breast cancer.

Some interventions are designed to serve the dual purpose of meeting local health needs and providing a model for other programs. The South Carolina Cardiovascular Disease Prevention Program, which is funded by CDC, is a learning laboratory for identifying the most successful ways to which state and local health departments can replicate community-based interventions. This program has incorporated public awareness campaigns, a speakers bureau, cooking classes, a television home-study course, blood pressure and cholesterol screening, self-help kits on various health topics, and walking trails in the community. The Community Chronic Disease Prevention Program works with health departments to develop programs that will alter high-risk behavior, such as high-cholesterol diet, particularly among minority populations. The aim is to extend these programs to other states and other chronic diseases.

The center is committed to creating a liaison between the major participants in chronic disease prevention in the United States so that skills, experiences, and resources can be shared. To this end, the center fosters interaction between state and local health departments, voluntary organizations concerned with chronic disease, the medical community, and federal health agencies. With the Association of State and Territorial Health Officials (ASTHO), CDC cosponsors an annual national Chronic Disease Conference where these groups can discuss the public health issues related to chronic disease. Other conferences on specific issues are held throughout the year and are open to interested parties. The center has also established a newsletter, *Chronic Disease Notes and Reports*, to provide a regular forum for communication between federal, state, local, voluntary, and other programs.

The state and local health departments and major voluntary health organizations have enthusiastically welcomed the formation of CCDPHP. ASTHO and its affiliates had urged CDC to provide just such a consolidation of programs so they could more easily work with their counterparts at CDC and get needed technical assistance. The voluntaries had encouraged CDC to provide more visible national leadership in the area of chronic disease. Working together will provide immense possibilities for success in improving the health status of Americans.

Nutrition Education Subcommittee Procedures

All nutrition publications and materials prepared for the public by any of the components of the NIH are to be brought to the attention of the NIH Nutrition Education Subcommittee for review and comment. Adherence by the institutes to the subcommittee's recommendations is required, and all revisions of publications/materials are to be brought to the attention of the Education Subcommittee chairperson before their final publication.

PROCESS

The ICD information officers and/or NCC members are to bring to the attention of the Education Subcommittee chairperson all nutrition publications/materials destined for the public when they are close to the final draft stages, prior to their review for institute clearance review.

- The Education Subcommittee is asked to review and comment on the draft and provide comments to the chairperson within 2 weeks. The comments are then collated and discussed at a meeting of the subcommittee in the presence of the appropriate initiating institute staff. The final comments evolving from the subcommittee meeting are then transmitted to institute staff and NCC members for action.
- Problems with incorporating the subcommittee's comments are to be discussed and resolved with the subcommittee chairperson and respective ICD-NCC representative. If such problems are not resolved, the entire NCC will be asked to provide comment. The revised version of the publication is to be brought to the attention of the chairperson to assure accuracy and consistency. Depending on the extent of the revision, a second review by the entire subcommittee may be required.
- After the publication has been cleared by the institute, the final revised version is to be brought to the attention of the Education Subcommittee chairperson.
- Sample copies of all printed publications and information regarding availability should be provided to the Education Subcommittee chairperson and the NCC office in order to keep up-to-date the list of nutrition publications available to the public from the various NIH institutes.

CONTENT

Each publication is reviewed for the following:

- Scientific accuracy. All information is based on the best current scientific evidence. Areas known to be controversial also need to be addressed to avoid misinterpretation by the public.
- Consistency with other NIH nutrition publications to avoid mixed messages.
- Compatibility with the *Dietary Guidelines for Americans*. Because the guidelines serve as the basis for all Federal dietary guidance to the general public, publications directed toward most healthy Americans must support the tenets of the dietary guidelines.
- Identification of the intended audience (e.g., adults, children, and etc.) and the ability to meet the specific needs of the intended target group, be it the healthy general public or other subpopulation groups (e.g., patient populations, minority groups, and etc.). For example, the reading level needs to conform to the needs of the target audience, and publications should be culturally relevant.
- Avoidance of mention of specific brand names of foods or other items that can be misconstrued as NIH endorsement.
- Appeal and clarity of the overall publication, title, graphs, illustrations, and charts to illustrate difficult concepts.

NIH Nutrition Publications Reviewed by the Nutrition Education Subcommittee

The publications listed below are available from the offices listed; all addresses are National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892.

National Cancer Institute

Office of Cancer Communications

Building 31, Room 10A18

Good News, Better News, Best News...Cancer Prevention	84-2671
What Black Americans Should Know About Cancer	82-1635
Diet, Nutrition, and Cancer Prevention...A Guide to Food Choices (intended for health professionals)	87-2711
Diet, Nutrition and Cancer Prevention...The Good News	87-2878
Eating for Life	88-3000

National Heart, Lung, and Blood Institute

Information Office

Building 31, Room 4A21

Questions About Weight, Salt and High Blood Pressure	84-1459
NHLBI Facts About Blood Cholesterol	88-2696
Healthy Heart Handbook for Women	87-2720
Eating for Life	88-3000
So You Have High Blood Cholesterol (intended for patients)	87-2922
Eating To Lower Your High Blood Cholesterol (intended for patients)	87-2920

National Institute on Aging

Information Office

Federal Building, Room 6C12

Be Sensible About Salt	Age Page
Osteoporosis: The Bone Thinner	Age Page
Dietary Supplements: More Is Not Always Better	Age Page
Nutrition: A Lifelong Concern	Age Page
Hints for Shopping, Cooking, and Enjoying Meals	Age Page

National Institute of Dental Research

Office of Communications

Building 31, Room 2C35

A Healthy Mouth for You and Your Baby	86-1255
Fluoride to Protect the Teeth of Adults	87-2329

National Institute of Diabetes and Digestive and Kidney Diseases

Information Office

Building 31, Room 9A04

Irritable Bowel Syndrome	87-693
Noninsulin-Dependent Diabetes (intended for patients)	87-241

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Information Office

Building 31, Room 4C05

Osteoporosis - Cause, Treatment, Prevention	86-2226*
(*Send a SASE for a single copy; for multiple copies, contact the office above for price list)	

National Institute of Child Health and Human Development

Information Office

Building 31, Room 2A32

Understanding Gestational Diabetes—A Practical Guide to a Healthy Pregnancy	89-2788
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NIH Task Force on the Nutrition Priority Area Year 2000 Health
Objectives for the Nation

Chairperson: Darla E. Danford, M.P.H., D.Sc., R.D.
DNRC

ICD*	Member
NCI	Ritva Butrum, Ph.D. Elaine Lanza, Ph.D.
NHLBI	Nancy Ernst, M.S., R.D.
NIDR	Joseph E. Ciardi, Ph.D.
NIDDK	Van S. Hubbard, M.D., Ph.D.
NICHD	Ephraim Y. Levin, M.D.
NIA	Ann W. Sorenson, Ph.D.
NIAMS	Stephen P. Heyse, M.D.
Nutrition Education Subcommittee Liaison	Karen Donato, M.S., R.D.

*Institute, Center, Division

Availability of Fish Oil Test Materials

FISH OIL TEST MATERIALS PROGRAM

The Fish Oil Test Materials Program is administered by the DNRC, NIH. The program was established in 1986 through the cooperation of the NIH, ADAMHA, and NOAA/DOC. This program has been designed to provide a long-term, consistent supply of quality-assured/quality-controlled test materials to researchers in order to facilitate the evaluation of the role that omega-3 fatty acids play in health and disease.

Fish Oil Test Materials Advisory Committee

A Fish Oil Test Materials Advisory Committee (FOTMAC) is cochaired by scientific staff from NIH and ADAMHA and is composed of scientists representing the funding agencies (NIH, ADAMHA), the research community, DOC, and the FDA. The FOTMAC provides scientific advice to the DOC regarding the types of materials needed by research scientists, shipping procedures for the materials, and additional quality control and production issues. The committee is advisory to the Fish Oil Test Materials Program on general programmatic issues such as future directions and has produced a manual on Good Laboratory Practices for the handling of polyunsaturated materials. In addition, the committee provided guidance to DOC during the production of the Drug Master File submitted to the FDA by the FOTMAC. Manuals on Analytical Methods for the Quality Assurance of Fish Oil, Production Methods/Safety and Distribution were produced by the DOC.

Fish Oil Test Materials Distribution Committee

A Fish Oil Test Materials Distribution Committee (FOTMDC) is composed of NIH and other Federal scientists who do not use these products. The FOTMDC processes the applications received from investigators on a quarterly basis, advises the DOC of applicants that have fulfilled the application process, and makes recommendations to DOC regarding the distribution of requested materials.

TEST MATERIALS CURRENTLY AVAILABLE

- EPA Ethyl Ester

The ethyl ester of EPA is prepared from vacuum-deodorized menhaden oil using transesterification, urea adduction and short-path distillation to yield an n-3 ethyl ester concentrate. The purified ethyl ester of EPA is attained by supercritical fluid CO₂ extraction from the n-3 ethyl ester concentrate followed by high performance liquid chromatography. The product contains >95% ethyl esters; of the ethyl esters EPA is 97%, other n-3's are <1%, n-6's are <1% and other fatty acids are <1%.

- DHA Ethyl Ester

The ethyl ester of DHA is prepared from vacuum-deodorized menhaden oil using transesterification, urea adduction and short-path distillation to yield an n-3 ethyl ester concentrate. The purified ethyl ester of DHA is attained by supercritical fluid CO₂ extraction from the n-3 ethyl ester concentrate followed by high performance liquid chromatography. The product contains >95% ethyl esters; of the ethyl esters DHA is 96%, other n-3's are <2%, n-6's are <1% and other fatty acids are <1%.

- **n-3 Ethyl Ester Concentrate**

The n-3 ethyl ester concentrate is prepared from vacuum-deodorized menhaden oil using transesterification, urea adduction and short-path distillation. The concentrate contains approximately 80% n-3 fatty acid ethyl esters (44% EPA, 24% DHA, 10-12% other n-3 fatty acid ethyl esters), 3% C18 (other than n-3), 6% C16 and the remainder as other esters. It contains 0.2 mg/g TBHQ as antioxidant, 2 mg/g tocopherols and 2.0 mg/g cholesterol. The concentrate is available in 1 g soft-gel capsules (100 capsules/bottle) or packaged in bulk in quantities suitable to investigators needs.

- **Placebo Ethyl Esters**

The ethyl esters of virgin olive oil are prepared by transesterification. The preparation contains approximately 70% oleic acid, 13% C16, and 15% C18 (<1% n-3) fatty acid ethyl esters. It contains 0.2 mg/g TBHQ as antioxidant and 2 mg/g tocopherols. The preparation is available in 1 g soft-gel capsules (100 capsules/bottle) or packaged in bulk in quantities suitable to investigators needs.

- **Deodorized Menhaden Oil**

Deodorized menhaden oil is prepared from oil that has been winterized and alkali refined; it is processed through a two-stage wiped-film evaporator to remove cholesterol, volatile oxidation products, and any traces of organic contaminants. The oil contains approximately 30% n-3 fatty acids in the triglyceride form, 14% EPA, 8% DHA, and 8% other n-3. It contains 0.2 mg/g TBHQ as antioxidant, 2 mg/g tocopherols and 2.0 mg/g cholesterol. The deodorized oil is available in 1 g soft-gel capsules (100 capsules/bottle) or is packaged in bulk quantities suitable to investigators needs. Special requests for antioxidant free oil may be entertained.

- **Placebo Oils**

Commercial preparations of corn, olive, and safflower oil have been soft-gel encapsulated to serve as placebos for the encapsulated menhaden oil. These oils contain 0.2 mg/g TBHQ as antioxidant and 2 mg/g tocopherols. The major fatty acids for each oil are corn (58% 18:2n-6, 26% 18:1n-9), olive (17% 18:2n-6, 57% 18:1n-9), and safflower (80% 18:2n-6, 9% 18:1n-9). They are available in 1 g soft-gel capsules (100 capsules/bottle). Investigators may request analysis of antioxidant and tocopherol levels in oil purchased for use as placebos for bulk menhaden oil.

APPLICATION PROCESS

To qualify to receive materials described in this announcement the applicant must 1) have a peer-reviewed research project indicating the need for the requested materials, and 2) submit a correctly completed application form and a signed waiver of liability. The committee will not be responsible for assessing the scientific merit of the application. Regulations on human subjects and animal research apply. In accordance with federal regulations, an IND number will be required for the use of these materials in human studies. The FOTMAC has established a drug master file at the FDA which includes manufacturing, chemical composition, and toxicological data relevant to these products. Investigators using NOAA/DOC materials may reference this file in order to expedite their IND requests. Availability of materials are contingent on DOC/NOAA production capabilities. When prioritization is necessary, the order will be 1) NIH/ADAMHA funded, 2) other U.S. government funded, 3) peer-reviewed, other funded, 4) NIH/ADAMHA approved, not funded, and 5) other.

The awarded materials are provided to investigators free of charge, except for international shipping charges. Requests for materials of amounts greater than 175 g/year of EPA ethyl ester and/or 100 g/year of DHA ethyl ester should not be submitted without prior discussion with the NMFS - Charleston Laboratory. For further information contact Ms. Patricia Fair at (803) 762-1200.

TEST MATERIALS AVAILABLE IN THE FUTURE

Test materials and their relevant application process will be announced in the "NIH Guide" as new materials become available.

OTHER INFORMATION

Additional information will be provided to the investigator in the form of complete quality assurance data for each lot of test material shipped, stability data, and storage instructions.

INQUIRIES AND APPLICATIONS

Investigators may obtain further information and apply for available fish oil test materials for relevant studies by requesting an application form from:

Fish Oil Test Materials Program Coordinator
Division of Nutrition Research Coordination
Building 31, Room 4B63
National Institutes of Health
Bethesda, Maryland 20892
301-496-2323

HNRIM System Classification Codes

The development of the Human Nutrition Research Information Management (HNRIM) System, which was established in 1982, began with the work of the NCC. Since 1977, the NCC has retrieved data on NIH projects with nutrition research and training components and their nutrition expenditures, based on the definition of human nutrition research developed by the NCC. The HNRIM System is managed by the DNRC, under the auspices of the ICHNR.

The Joint Subcommittee on Human Nutrition Research, operating out of the Office of Science and Technology Policy in the Executive Office of the President, expanded the NIH definition and data collection system to include the human nutrition research activities supported by participating Federal agencies, and developed a system of 34 data classification categories for human nutrition research. In FY 1985, Code 35, "Parenteral, Enteral, and Elemental Nutrition," was added, and the NIH Special Interest Areas were assigned to codes 51-56. The FY 1989 NIH nutrition research program is presented in accordance with this classification system, which is used by the HNRIM System.

The nutrition projects in the system are classified under five major areas, and research in the biomedical and behavioral sciences is subclassified under three major components. The system is subsequently divided into 35 categories. Each nutrition research project is assigned classifications, and as many classifications as are needed are chosen in order to adequately identify all major nutrition aspects of the research project. Additional codes are assigned to special interest areas of the NIH.

I. Research in the Biomedical and Behavioral Sciences

A. Research on Normal Nutritional Requirements Throughout the Life Cycle

The following five categories are included because of the importance to health promotion of establishing normal nutritional requirements throughout the life cycle, and the differing needs of individuals at various stages of the life cycle.

Research activities relevant to normal nutrition at specific stages of the human life cycle should be assigned to classifications 1-5.

1. Maternal Nutrition

2. Infant and Child Nutrition (0-12 years) (Includes the low birth weight infant)

3. Adolescent Nutrition (13-18 years)

4. Adult Nutrition (19-65 years)

5. Nutrition of the Elderly (65+ years)

B. Diseases and Conditions

Research on the role of nutrition in the prevention, amelioration, and treatment of diseases and conditions should be assigned to categories 6-16.

Because of the importance of appropriate nutritional support of the patient in the treatment of disease, the category of "parenteral, enteral, and elemental nutrition" has been added in this subsection as code 35.

6. Cardiovascular Disease and Nutrition

7. Cancer and Nutrition

8. Other Diseases and Nutrition (e.g., osteoporosis, diabetes, etc.)

9. Trauma (Including Burns) and Nutrition

10. Infection--Immunology and Nutrition

11. Obesity, Anorexia, and Appetite Control

12. Genetics and Nutrition

13. Nutrition and Function (Includes mental, psychomotor, and work performance; environmental stress)

***14. Nutrient Interactions** (Includes nutrient-nutrient interactions, nutrient-drug interactions, nutrient-toxicant interactions, and nutrient toxicity)

15. Other Conditions and Nutrition

***16. Nutritional Status** (Includes research on methods for the determination of nutritional status and surveillance: dietary history and food consumption, biochemical determinants, anthropometry, and clinical examination)

35. Parenteral, Enteral, and Elemental Nutrition

C. Nutrient Metabolism and Metabolic Mechanisms at the Cellular and Subcellular Levels

Categories 17-25, 14, and 27 classify research by nutrient variables; these categories should be used to indicate the nutrient variables in research classified elsewhere; and classify biochemical, subcellular, cellular, and animal research such as studies of nutrient mechanisms and metabolism not related to specific diseases, conditions, or stages of the life cycle.

17. Carbohydrates

18. Lipids (Fats and Oils) (Includes essential fatty acids, lipo- and apoproteins)

19. Alcohols

(Includes ethanol, sorbitols, and other alcohols used as components in synthetic and semisynthetic foods)

20. Proteins and Amino Acids

(Includes essential as well as nonessential amino acids such as taurine and carnitine)

21. Vitamins

(Includes vitamins A, C, B₆, B₁₂, D, E, K, thiamin, riboflavin, niacin, folacin, biotin, and pantothenic acid)

22. Minerals and Essential Trace Elements

(Includes calcium, phosphorus, magnesium, iron, zinc, iodine, copper, manganese, fluoride, chromium, selenium, and molybdenum)

23. Water and Electrolytes

(Includes sodium, potassium, and chloride)

24. Fiber**25. Other Nutrients in Food**

(Such as cobalt, nickel, vanadium, silicon, tin, arsenic, cadmium, choline, lecithin, and various growth factors)

***14. Nutrient Interactions**

(Includes nutrient-nutrient interactions, nutrient-drug interactions, nutrient-toxicant interactions, and nutrient toxicity)

***27. Bioavailability of Nutrients**

(Includes methods for the determination of bioavailability of nutrients)

II. Research in Food Sciences

Categories 26-29 should be used for research in the nutritional aspects of food sciences.

26. Food Composition

(Includes nutritional quality, nutrient content, and research on methods of analysis for nutrients and fiber)

***27. Bioavailability of Nutrients**

(Includes methods for the determination of bioavailability of nutrients)

28. Effects of Technology on Acceptability and Nutritional Characteristics of Foods and Diets

(Includes the beneficial and adverse effects of varietal and species differences, harvest and post-harvest technology, retail food practices, food processing, handling, preservation, and home cooking)

29. Other Research in Food Sciences

III. Research on Nutrition Monitoring and Surveillance of Populations

30. Food Consumption Surveys

(Includes research on methods for determination of food consumption and its trends, and research utilizing data derived from such surveys)

31. Studies of Dietary Practices, Food Consumption Patterns, and Their Determinants

***16. Nutritional Status**

(Includes research on methods for the determination of nutritional status and surveillance: dietary history and food consumption, biochemical determinants, anthropometry, and clinical examination)

IV. Research in Nutrition Education

Categories 32-33 encompass research in nutrition education.

32. Studies on Methods for Informing and Educating the Public About Nutrition, Health, and Dietary Practices and for Countering Nutrition Misinformation

(Includes studies on methods for informing and educating professionals in these areas)

33. Other Research in Nutrition Education

V. Research on the Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition

34. Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition

VI . NIH Special Interest Areas

Codes 51-56 have been assigned to special interest areas of the NIH.

51. Prevention of Disease

52. International Research

53. Epidemiological Research

54. Education for Professionals

55. Education for the Public

56. Clinical Trials

*Codes marked by an asterisk are applicable to more than one class.

NIH Award Mechanisms

The NIH relies on three major instruments for accomplishing its program goals through the efforts of scientists outside the NIH. The mechanisms are financial assistance awards (grants and cooperative agreements) and acquisition awards (contracts).

Financial Assistance Awards

Grants. Grants for health-related research projects or activities make up the largest category of funding provided by the NIH. These grants encourage and support meritorious projects or programs in all scientific fields related to health and span the spectrum from basic and applied research in laboratory and clinical settings to the evaluation, demonstration, and dissemination of new medical technologies. In addition, grants are awarded to create and sustain certain special resources or facilities for such research.

Grants are awarded to nonprofit organizations and institutions, governments and their agencies, and to individuals and for profit organizations for the support of research in health, medicine, and allied fields. Grants provide funds for salaries, equipment, supplies, travel, and other allowable direct costs of the research as well as for indirect costs. Through the grant mechanism, the NIH supports research projects, centers, career development and other research programs.

Grants are used when the idea for the research or training project is initiated by the investigator; when no substantial program involvement is anticipated between the funding ICD and the recipient during performance of the activity; and there is no expectation on the part of the funding ICD for delivery of a specified product or service. A grant may provide funds for essentially all reasonable costs of the activity. Grant applications may request, in most instances, an approximate amount of financial support and the duration of time, usually no more than 5 years, needed to complete the project. Funding is accomplished in annual increments.

Most applications for grant support originate with an individual investigator who develops a proposed plan for research or research training within an area of interest to the NIH. In addition, the NIH employs a variety of mechanisms to stimulate submission of applications in areas of high priority or special concern, including program announcements (PAs) and requests for applications (RFAs).

Cooperative Agreements. Cooperative agreements are similar to grants in that they are awarded by NIH to assist and support research and related activities. They differ, however, in that grants require minimal involvement of the awarding ICD during the performance of project activities, but cooperative agreements give a substantial programmatic, i.e., scientific/technical, role to the ICD. This role may involve cooperation or coordination to assist awardees in carrying out the project or review and approval of certain processes/phases in the scientific management of the project.

Policies and procedures for application, review, and administration of cooperative agreements are similar to those for grants. An important difference, however, is that the unit issues a specific PA or RFA describing the program, functions, or activities that it proposes to support by cooperative agreement and the nature of the proposed staff involvement. Terms and conditions, above and beyond those required for the normal stewardship of grants, must be negotiated in order to establish the rights, responsibilities, and duties of the prospective awardee and the NIH awarding unit, based on the terms and conditions outlined in the PA or RFA.

Review Process. Applications are subjected to a peer review process that is based upon two sequential levels of review, both of which are required by law. In general, applications for various types of financial assistance awards are received and reviewed three times per year. The first level of review is performed by initial review groups (IRGs), often called study sections, composed of at least 75 percent non-Federal scientists

selected for their competence in particular scientific areas. An NIH health scientist administrator serves as executive secretary of the review group. The task of the IRGs is to evaluate the grant application for scientific and technical merit.

In considering the scientific merit of each application, the members of the IRG assess:

- scientific, technical, or medical significance and originality of the proposed research;
- appropriateness and adequacy of the experimental approach and methods to be used;
- qualifications and experience of the principal investigator and staff in the area of proposed research;
- reasonable availability of resources necessary to the proposed research;
- reasonableness of the proposed budget and duration in relation to the proposed research; and
- where an application involves activities that could have an adverse effect upon humans, animals, or the environment, the adequacy of the proposed means for protecting against such effects.

For each application, a recommendation of approval, disapproval, or deferral for additional information is made by majority vote. In addition, for each application recommended for approval, each member of the IRG individually records a numerical rating that reflects a personal evaluation of the relative scientific merit of the proposed research or training. Members are asked to base the numerical rating on an adjectival scale from 1.0, most meritorious (outstanding), to 5.0, the least meritorious (acceptable) rating, with increments of 0.1.

After the meeting, the executive secretary averages the individual reviewer's ratings for each favorably recommended application and multiplies by 100 to provide a three-digit rating that is the priority score. In addition to the priority score, a percentile rank is displayed on the summary statement of those applications reviewed by the IRG. The percentile represents the relative position or rank of each priority score among the scores assigned by the particular IRG. The percentile rank of priority scores guides the councils and institutes in their decisions about which approved applications are funded.

The executive secretary prepares a summary statement for each application and forwards it to the appropriate ICD for review by its council or board. A copy of the summary statement is also automatically sent to the principal investigator by the ICD. The summary statement contains a description and critique of the proposed activity, an explanation of the recommendation of the IRG, a recommended budget, and notations about any special points such as a split vote or a potentially hazardous experimental procedure.

The second level of review of applications is made by the national advisory council or board associated with the awarding ICD. These groups are composed of both scientific and lay representatives who are chosen for their expertise, interest, or activity in matters related to the individual ICD missions. Council or board recommendations are based on judgments about scientific merit and relevance to ICD program goals. In general, the NIH may make an award only if the application has been recommended for approval by both an IRG and a national advisory council or board.

Acquisition Awards

Contracts. NIH awards research and development (R&D) contracts to academic institutions and other non-profit and commercial organizations for specific scientific inquiry directed towards particular areas of research and development needed by the NIH or U.S. government. In these circumstances the NIH wishes to utilize advances in knowledge and technology to search for solutions to specific questions. Contract performance is monitored closely by NIH to ensure accomplishment of contract goals for the benefit of or use by the awarding ICD, the NIH, or the government.

Most NIH R&D contracts are of the cost-reimbursement type, where the NIH pays contractors allowable, allocable, and reasonable costs in performing the project. In addition to reimbursable costs, a fee may be paid where appropriate.

The review process for solicited R&D contracts differs from that for grants in that all offerers respond to a Government-defined statement of work contained in a solicitation document called a request for proposal (RFP). Proposals responding to the solicitation are evaluated against fixed evaluation criteria specified in the RFP. Consistent with statutory and regulatory requirements for peer review of NIH solicited contract projects, the concepts of each requirement and the contract proposals are evaluated by scientific peer review groups composed of at least 75 percent non-Federal advisors who provide recommendations regarding the merits of the basic purpose, scope, and objectives of proposed projects, and the relative merits of each proposal. In order to reach all segments of the scientific community, contract opportunities and requirements are advertised as widely as possible. Solicitation announcements appear in the *Commerce Business Daily*. (Subscriptions are available from the Superintendent of Documents, Government Printing Office, Washington, D.C. 20402.) Announcements of RFP availability also are published in the "NIH Guide for Grants and Contracts." Some project solicitations also may appear in scientific and medical journals or other pertinent publications.

R&D contract proposals responding to NIH solicitations undergo review by advisory peer evaluation groups whenever RFPs seek offerers for innovative and original approaches to accomplish tasks described in our solicitations. All proposals are evaluated strictly in accordance with evaluation criteria specified in the RFP. All of the tasks should be accomplished. All proposals are evaluated strictly in accordance with the evaluation criteria indicated in the RFP.

Recommendations of peer reviewers, and the results of separate NIH staff evaluations of technical and cost proposals, provide the basis for negotiations with offerers in a competitive range. At the conclusion of these discussions, offerers are requested to submit a best and final offer, which then serves as the basis for selection of offerers for award(s).

ICDs occasionally make awards in response to unsolicited contract proposals when they meet specific NIH program needs and when adequate justification exists for a noncompetitive award. In these instances, peer reviews may simultaneously evaluate both the concept and the approach for the proposed project. Subsequent evaluations and negotiations are similar to those for solicited proposals.

Clinical Trials

Clinical trials in nutrition are supported by each of the major mechanisms discussed above—research grants, contracts, and cooperative agreements. A clinical trial is defined as a scientific research activity undertaken to define, prospectively, the effect and value of prophylactic/diagnostic/therapeutic agents, devices, regimens, procedures, etc., applied to human subjects. The study must be prospective, and intervention of some sort must occur. The number of cases or patients depends on the hypothesis being tested, but must be sufficient to permit anticipation of a definite, statistically significant result. Phase I, feasibility, or pilot studies are excluded by definition.

Career Development Awards

Workforce development in nutrition research is enhanced through such mechanisms as the Modified Research Career Development Awards, Academic/Teacher Awards, Clinical Investigator Awards, Physician Scientist Awards, and the Dentist Scientist Awards. Brief descriptions of these awards follow.

- Modified Research Career Development Awards foster the development of young scientists with outstanding research potential for careers of independent research in the sciences related to health.

- Academic/Teacher Awards create and encourage a stimulating approach to disease-specific curricula that will attract high-quality students, foster academic career development of promising young teacher-investigators, develop and implement excellent multidisciplinary curricula through an interchange of ideas, and enable the grantee institution to strengthen its existing teaching program. The academic and teacher investigator awards are not used by all of the institutes.
- Clinical Investigator Awards provide the opportunity for promising medical scientists (with demonstrated aptitude to develop into independent investigators) or faculty members to pursue research aspects of categorical areas applicable to the awarding unit, and aid in filling the important academic faculty gap in these shortage areas within health professional institutions of the country.
- Physician Scientist Awards (Individual) support a newly trained clinician or clinically trained dentist nominated by an institution for the development of independent research skills and experience in a fundamental science.
- Dentist Scientist Awards (individual and institutional) support newly trained dentists to enhance their clinical training and obtain basic science research training.

Training Grants and Fellowships

The NIH supports the training of scientists for careers in the behavioral and biomedical sciences. Training opportunities are provided primarily through National Research Service Awards (NRSAs) and Fogarty International Fellowships.

National Research Service Awards. The major objectives of these awards are 1) to increase the number of individuals trained for research and teaching in specifically designed biomedical areas, and 2) to improve the environment in which the biomedical training is conducted. NRSA awards are made to U.S. citizens, noncitizen nationals, or individuals that have been lawfully admitted to the United States for permanent residence. Several of the most common types of NRSA awards are described below.

- Postdoctoral individual NRSAs, commonly known as "fellowships," are awarded to provide postdoctoral research training to qualified individuals who have received a Ph.D., M.D., D.D.S., or equivalent degree. The award provides the opportunity to carry out supervised research to enable biomedical scientists, clinicians, and others to broaden their scientific backgrounds and expand their potential for research in health-related areas. Each applicant must arrange to work with a particular sponsor affiliated with an institution that has the staff and facilities needed for the proposed training. The institutional setting may be a domestic or foreign nonprofit, private, or public institution, including NIH and ADAMHA.
- Institutional NRSAs, commonly known as "training grants," are awarded to domestic nonprofit, private, and non-Federal public institutions to support a training program in biomedical research at the predoctoral and postdoctoral levels. The applicant institution must have or be able to develop the staff and facilities required for the proposed program, and is responsible for the selection and appointment of trainees. Institutional grants may be made for periods up to 5 years and may be renewed. However, an individual may not receive more than 8 years of support in the aggregate from an NRSA (5 years predoctoral support and 3 years postdoctoral support) unless a waiver is granted by the responsible Public Health Service agency.
- Senior fellowships are designed to provide opportunities for experienced scientists to make major changes in the direction of their research careers, to acquire new research capabilities, to broaden their scientific background, to enlarge their command of an allied research field, or to take time from regular professional responsibilities to increase their capabilities for engaging in health-related research. Investigators who hold a doctorate or equivalent degree and have had at least 7 subsequent years of relevant research or professional experience may apply for senior fellowships. The award is granted for 1 year, with continued support not to exceed 24 months contingent upon the research training plan, satisfactory progress and the availability of funds.
- Fogarty International Fellowships. To further international cooperation and health research, the Fogarty International Center provides for and administers International Postdoctoral Fellowship programs for foreign scientists to study in the U.S. and for U.S. scientists to study abroad.

Information Sources at the NIH

The "NIH Guide for Grants and Contracts" describes programs at the NIH, announces new programs, RFAs, and RFPs, and provides policy guidance. Copies of the Guide may be found in many research and medical libraries. To request the Guide or for general information on NIH extramural programs, contact:

Institutional Liaison Office
Office of Extramural Research
National Institutes of Health
Building 31, Room 5B31
Bethesda, Maryland 20892
301-496-5366

The Office of Grants Inquiries in the Division of Research Grants serves as a focal point for information on NIH grant programs and application procedures. Relevant publications and single copies of application kits (if not available at an organization's application control office) may be obtained from:

Office of Grants Inquiries
Division of Research Grants
National Institutes of Health
Westwood Building, Room 449
Bethesda, Maryland 20892
301-496-7441

Questions regarding the extramural programs of a particular ICD should be directed to the awarding unit concerned; addresses and telephone numbers of ICD nutrition program contacts are listed in section 2. In addition, the DNRC and the NCC publish a brochure entitled *Nutrition Research at the NIH* for extramural scientists and potential grantees. To obtain a copy, contact:

Division of Nutrition Research Coordination
National Institutes of Health
Building 31, Room 4B63
Bethesda, Maryland 20892
301-496-9281

ADA	American Dietetic Association
ADAMHA	Alcohol, Drug Abuse, and Mental Health Administration
AHA	American Heart Association
AID	Agency for International Development
AIDS	acquired immunodeficiency syndrome
ALD	adrenoleukodystrophy
AMD	age-related macular degeneration
AMN	adrenomyeloneuropathy
AMS	Agriculture Marketing Service
AOA	Administration on Aging
APHA	American Public Health Association
ARIC	Atherosclerosis Risk in Communities
ARS	Agricultural Research Service
ASTHO	Association of State and Territorial Health Officials
ASTPHNPD	Association of State and Territorial Public Health Nutrition Program Directors
ATBC	alpha-tocopherol, beta-carotene
ATP	adenosine triphosphate
BLSA	Baltimore Longitudinal Study of Aging
BMI	body mass index
BMR	basal metabolic rate
BPD	bronchopulmonary dysplasia
CALGB	Cancer and Leukemia Group B
CARDIA	Coronary Artery (Disease) Risk Development in (Young) Adults
CATCH	Child and Adolescent Trial for Cardiovascular Health
CC	Clinical Center
CCDPHP	Center for Chronic Disease Prevention and Health Promotion
CDC	Centers for Disease Control
CFSAN	Center for Food Safety and Applied Nutrition
CHD	coronary heart disease
CNRU	Clinical Nutrition Research Unit
CNS	central nervous system
CPRP	Cancer Prevention Research Program
CRIS	Current Research Information Service
CVD	cardiovascular disease
DCRT	Division of Computer Research and Technology
DCT	Division of Cancer Treatment
DDE	dichlorodiphenyldichloroethylene
DDT	dichlorodiphenyltrichloroethane
DFMO	difluoromethylornithine
DHA	docosahexaenoic acid
DHHS	Department of Health and Human Services
DISC	Dietary Intervention Study in Children
DLA	Division of Legislative Analysis
DNA	deoxyribonucleic acid
DNRC	Division of Nutrition Research Coordination
DOC	Department of Commerce
DOD	Department of Defense
DRG	Division of Research Grants
DRR	Division of Research Resources
DRS	Division of Research Services

DTS	Division of Technical Services
DZ	dizygotic
ECG	electrocardiogram
EDI	Eating Disorder Inventory
EP	Extramural Program
EPA	eicosapentaenoic acid
ERS	Economic Research Service
ES	Extension Service
ESRD	end-stage renal disease
FASEB	Federation of American Societies for Experimental Biology
FDA	Food and Drug Administration
FFF	foreign-funded fellowship
FFV	Factored Food Vocabulary
FIC	Fogarty International Center
FNS	Food and Nutrition Service
FOTMAC	Fish Oil Test Materials Advisory Committee
FOTMDC	Fish Oil Test Materials Distribution Committee
FOTMP	Fish Oil Test Materials Program
FSA	Family Support Administration
FSIS	Food Safety and Inspection Service
FY	fiscal year (October 1 through September 1)
GC/MS	gas chromatography/mass spectrometry
GCRC	General Clinical Research Centers
GFR	glomerular filtration rate
GI	gastrointestinal
GRC	Gerontology Research Center
GTO	glycerol trioleate
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HMG CoA	3-hydroxy-3-methylglutaryl coenzyme A
HNIS	Human Nutrition Information Service
HNRIM	Human Nutrition Research Information Management
HPLC	high pressure liquid chromatograph
HRSA	Health Resources Services Administration
ICD	Institute, Center, Division
ICHNR	Interagency Committee on Human Nutrition Research
ICNM	Interagency Committee on Nutrition Monitoring
IHS	Indian Health Service
IL-1	interleukin-1
IRBP	interphotoreceptor retinoid-binding protein
IRF	international research fellowship
IRG	Initial Review Group
IRP	Intramural Research Program
JNC	Joint National Committee
LBM	lean body mass
LDL	low density lipoprotein
LEM	leukocyte endogenous mediator
LNAA	large neutral amino acids
LRC	Lipid Research Clinic
MDRD	Modification of Diet in Renal Disease
MEC	mobile examination center

MONICA	Multinational Monitoring of Trends and Determinants in Cardiovascular Disease
MOU	memorandum of understanding
NaCl	sodium chloride
NAD	nicotinamide adenine dinucleotide
NAL	National Agricultural Library
NASA	National Aeronautics and Space Administration
NCC	Nutrition Coordinating Committee
NCCTG	North Central Cancer Treatment Group
NCEP	National Cholesterol Education Program
NCHS	National Center for Health Statistics
NCI	National Cancer Institute
NCNR	National Center for Nursing Research
NCRR	National Center for Research Resources
NEC	necrotizing enterocolitis
NEI	National Eye Institute
NES	Nutrition Education Subcommittee
NGHS	National Growth and Health Study
NHANES	National Health and Nutrition Examination Survey
NHBPEP	National High Blood Pressure Education Program
NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute on Aging
NIAAA	National Institute of Alcoholism and Alcohol Abuse
NIADDK	National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal Intensive Care Unit
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIDR	National Institute of Dental Research
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NINDS	National Institute of Neurological Disorders and Stroke
NLM	National Library of Medicine
NMFS	National Marine Fisheries Service
NNMS	National Nutrition Monitoring System
NOAA	National Oceanic and Atmospheric Administration
NPB	Nutrition Policy Board (DHHS)
NRSA	National Research Service Award
NSF	National Science Foundation
NTD	neural tube defect
NTP	National Toxicity Program
OC	Office of Communications
OD	Office of the Director
ODP	Office of Disease Prevention
ODPHP	Office of Disease Prevention and Health Promotion (DHHS)
OHDS	Office of Human Development Services
OMB	Office of Management and Budget
ORS	Office of Research Services

OSTP	Office of Science and Technology Policy
PAHO	Pan American Health Organization
PAs	program announcements
PATCH	Planned Approach to Community Health
PCM	protein-calorie malnutrition
PHS	Public Health Service
PKU	phenylketonuria
PRC	Peoples' Republic of China
PTH	parathyroid hormone
R&D	research and development
RDA	recommended dietary allowance
RDS	respiratory distress syndrome
RFAs	requests for applications
RFLP	restriction-fragment-length polymorphism
RFPs	requests for proposals
RNA	ribonucleic acid
RPRC	Regional Primate Research Centers
SCOR	Specialized Centers of Research
SEAL	Sea, Air, and Land
SIF	senior international fellowship
SPRA	Special Program for Research on Aging
TBHQ	tertiary butyl hydroquinone
TBK	total body potassium
TNF	tumor necrosis factor
TPN	total parenteral nutrition
UCLA	University of California, Los Angeles
USARIEM	U.S. Army Research Institute of Environmental Medicine
USDA	U.S. Department of Agriculture
UWL	unstirred water layer
VA	Department of Veterans Affairs
VLBW	very low birth weight
VLCFA	very long chain fatty acids
WHO	World Health Organization



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